













The background of the slide is a blurred photograph of a surgeon in an operating room. The surgeon is wearing a white surgical cap, a face mask, and blue scrubs. They are leaning over a patient, with their hands near the surgical site. The lighting is bright, typical of an operating room. The image is slightly out of focus, emphasizing the text in the foreground.

# TITIN

... its role in cardiomyopathy



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**Whenever I found out anything remarkable, I have thought it my duty to put down my discovery on paper, so that all ingenious people might be informed thereof.** Antony van Leeuwenhoek. Letter of June 12, 1716



**TITIN** is the largest known protein with a megaDalton molecular weight and a contour length greater than one micron.

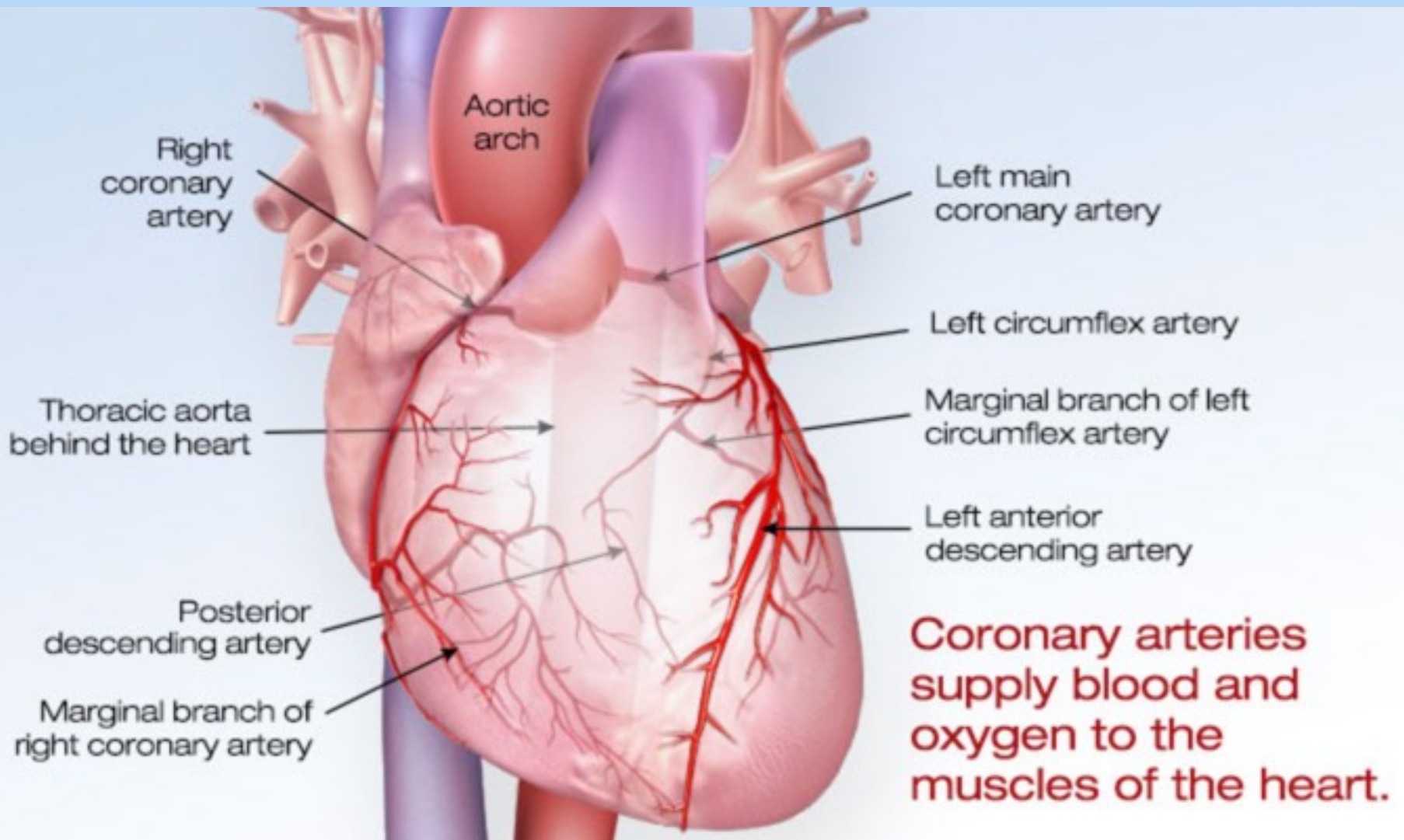
One molecule of titin spans half a sarcomere connecting both the M-line and the Z-disc.

This giant protein plays a pivotal role in myocardial passive stiffness, structural integrity and stress-initiated signaling pathways.

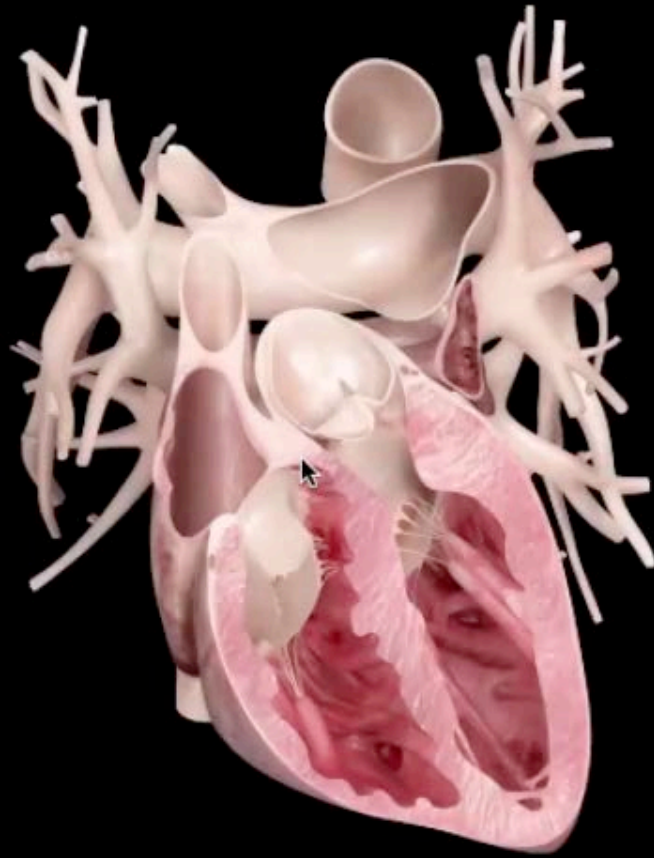








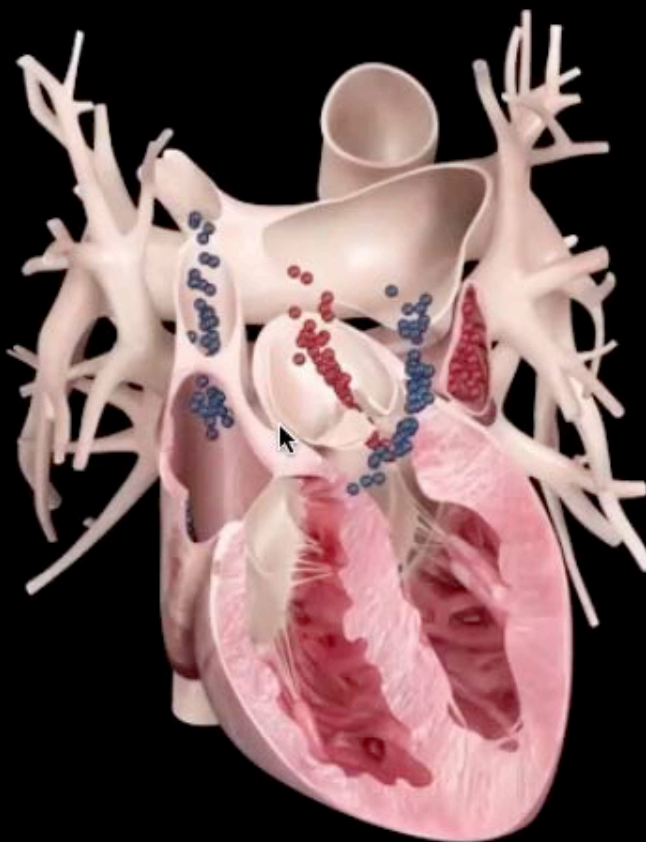




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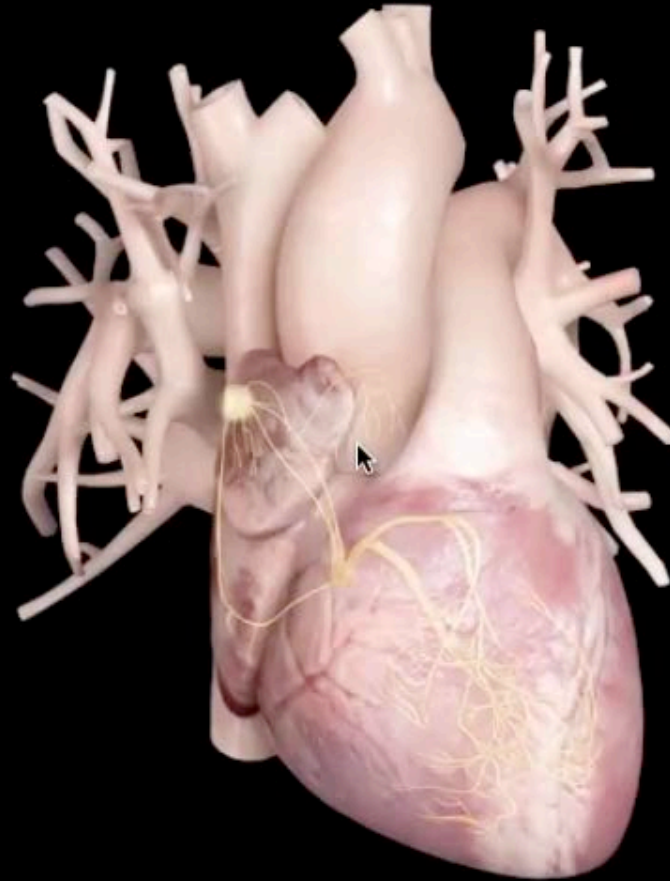


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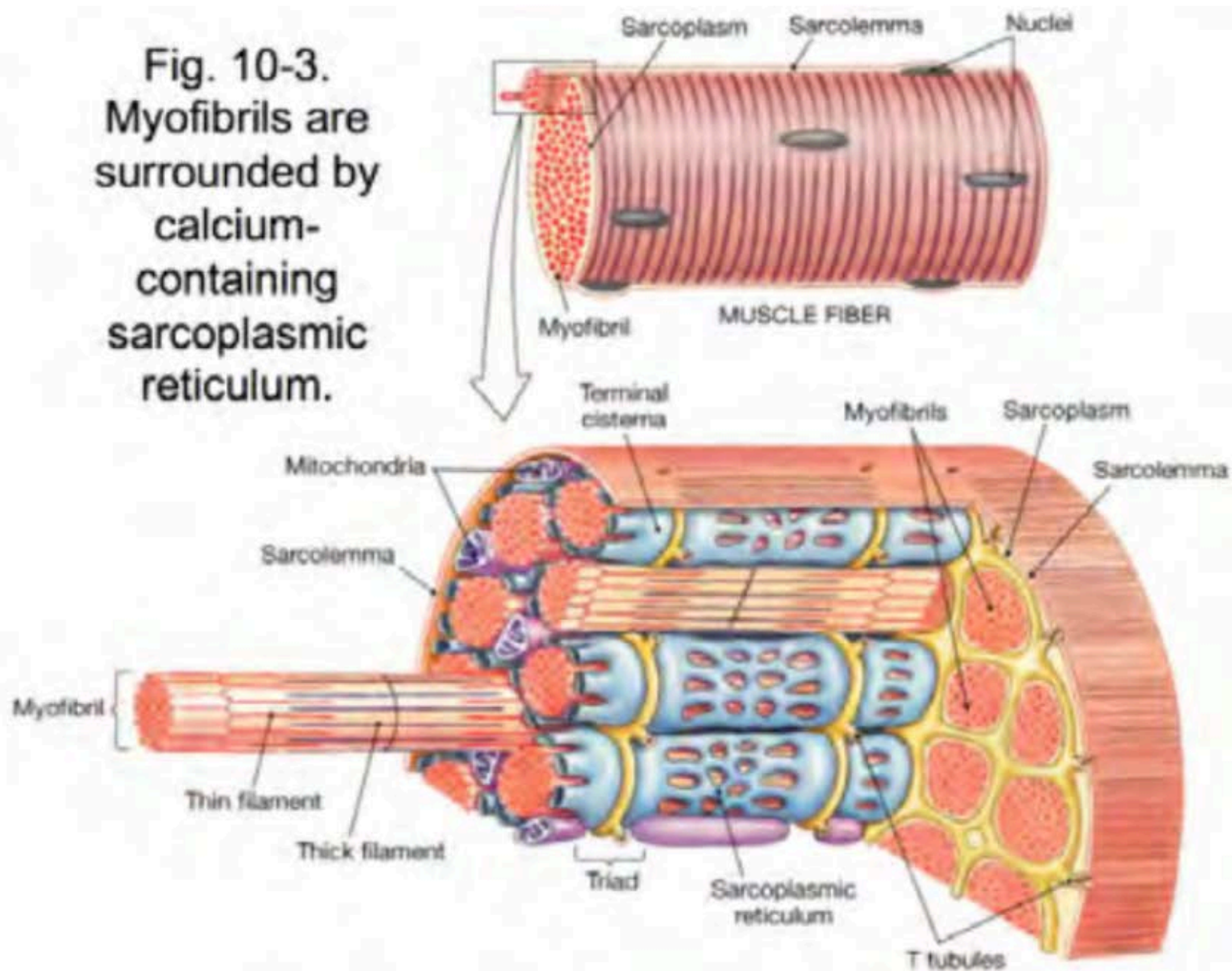


*We shall not cease from exploration  
And the end of all our exploring  
Will be to arrive where we started  
And know the place for the first time.*

T.S. Eliot --- "Little Gidding" ... *Four Quartets*



Fig. 10-3.  
Myofibrils are  
surrounded by  
calcium-  
containing  
sarcoplasmic  
reticulum.

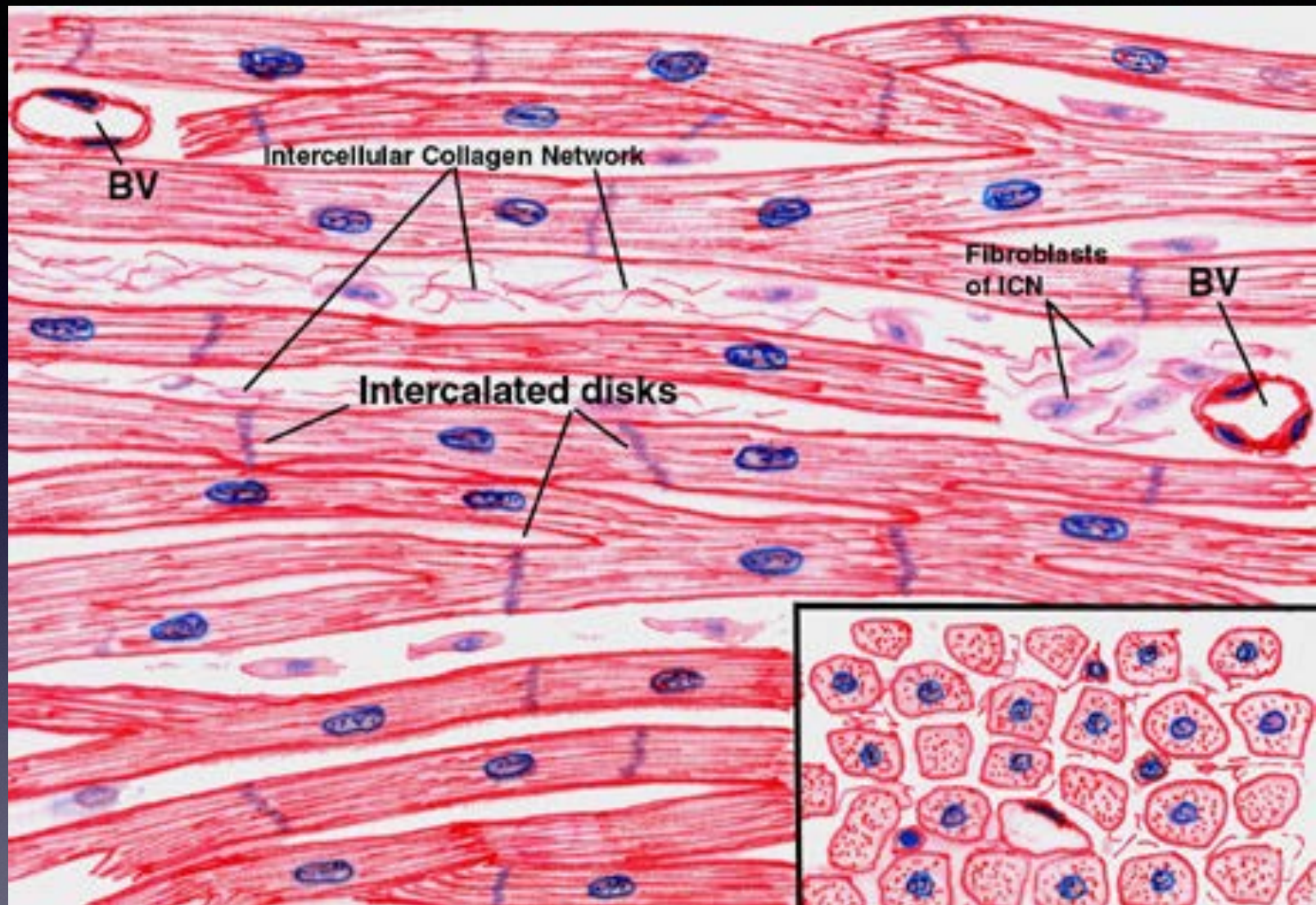






human myocardium





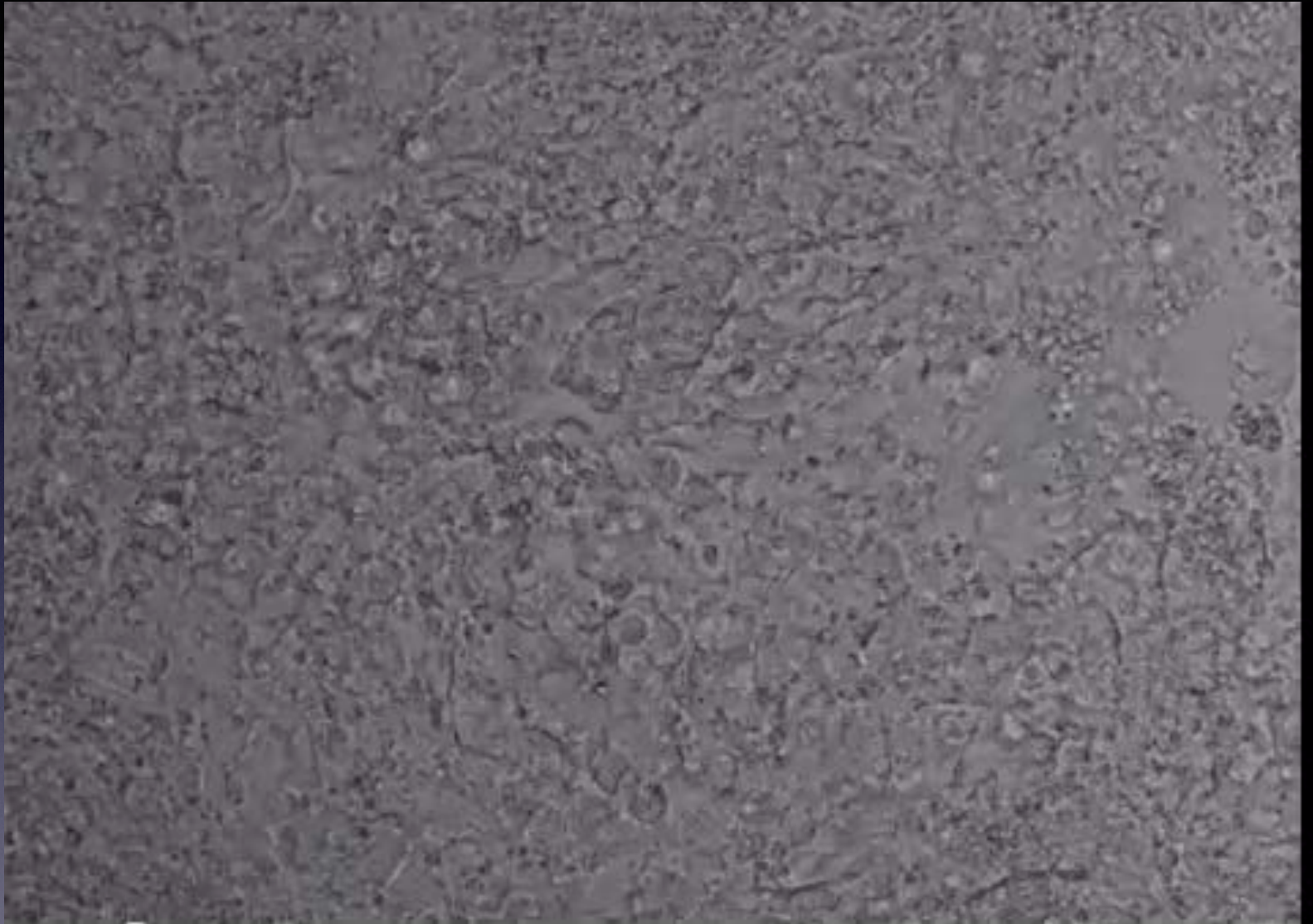
**myocardial cell : 50% engine (contractile elements),  
33% powerhouse (mitochondria) ... by volume**





**isolated myocardial cells** ( wait briefly for video action)

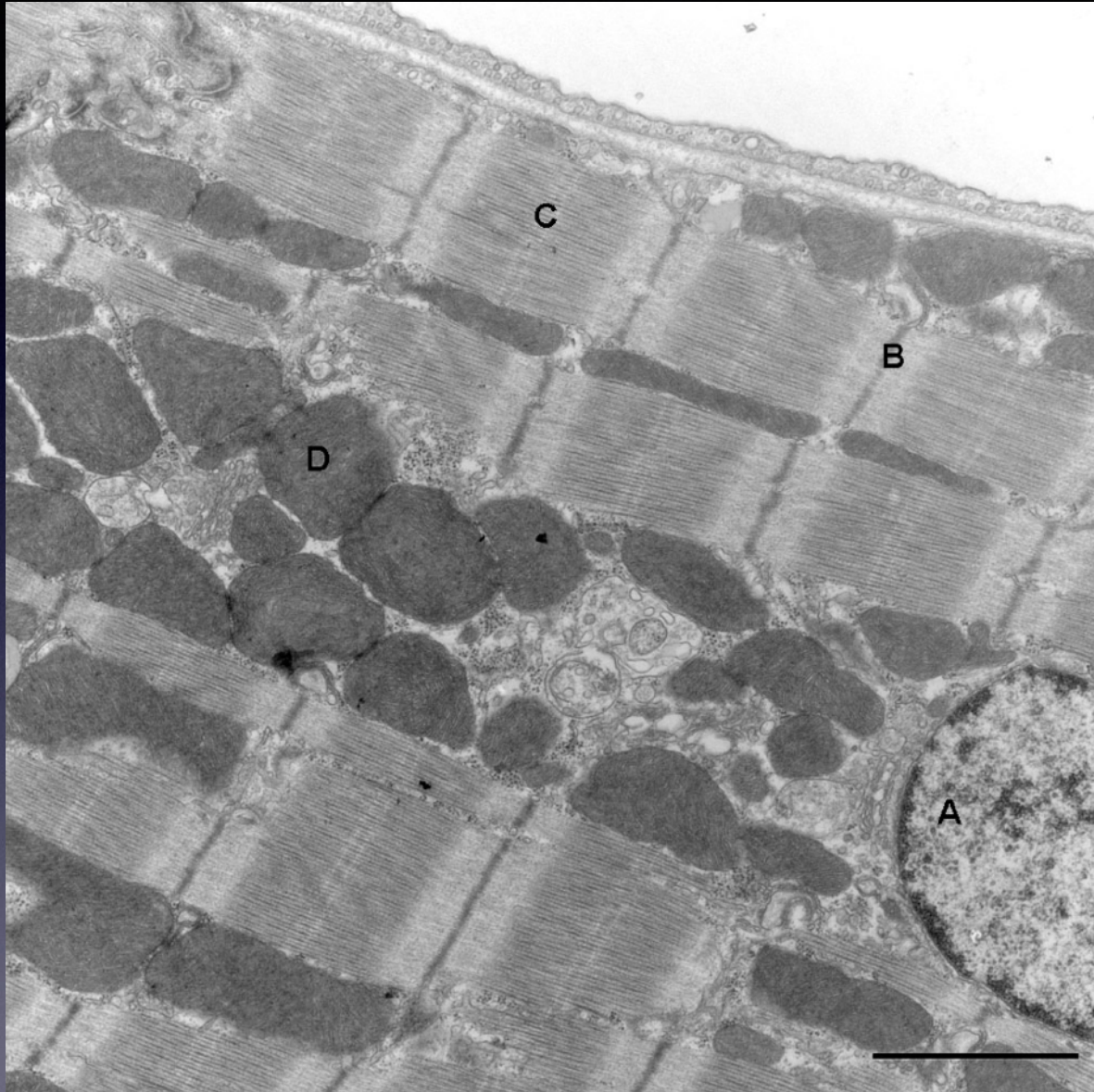




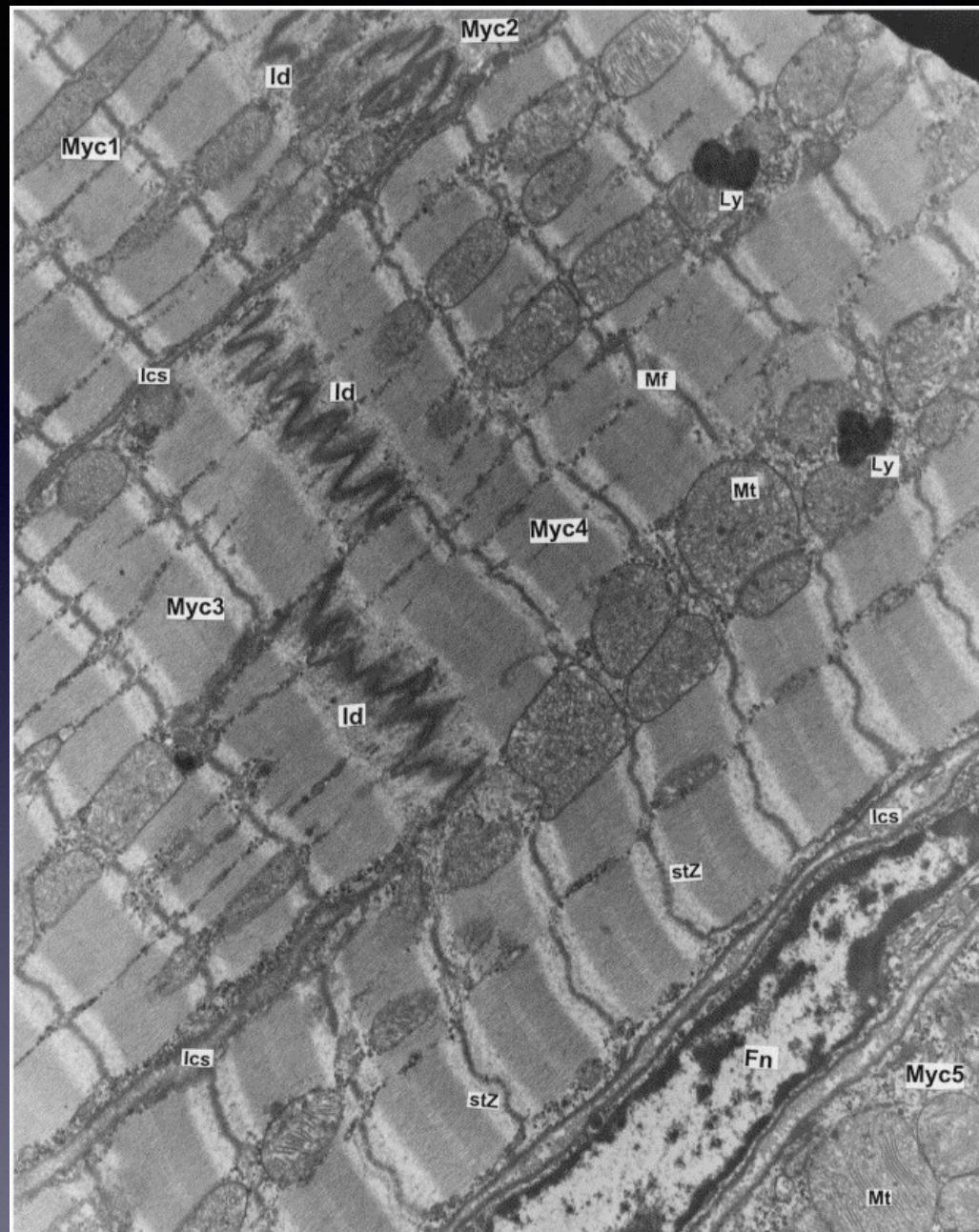
**myocardial cells in tissue culture**

( wait briefly for video action )



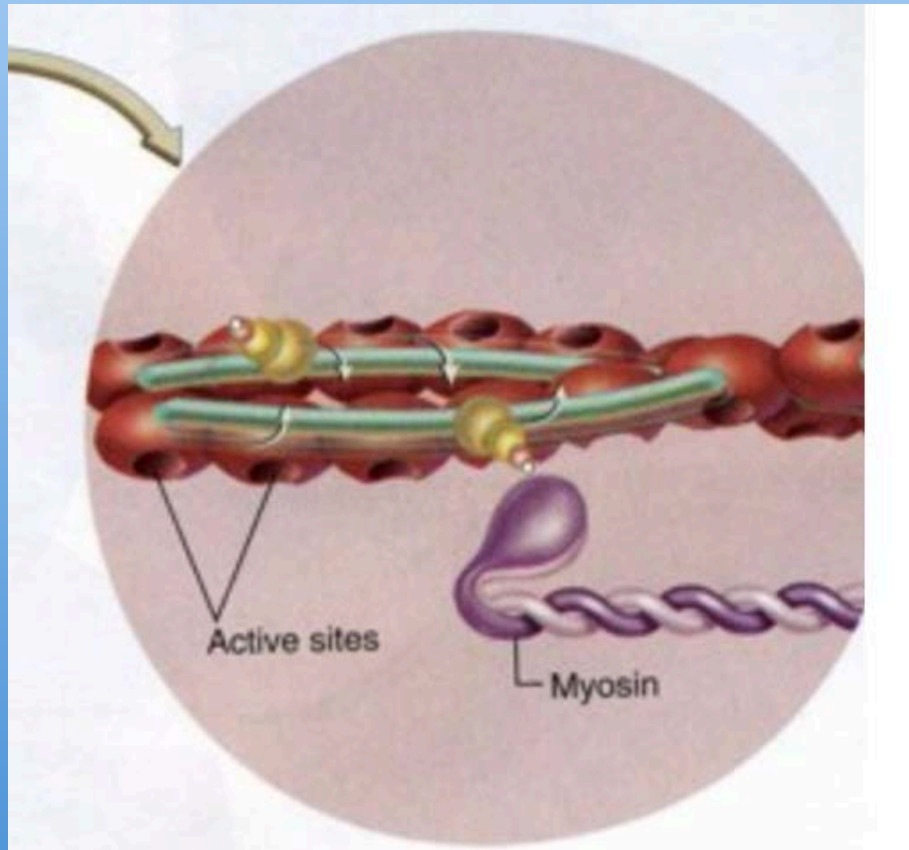






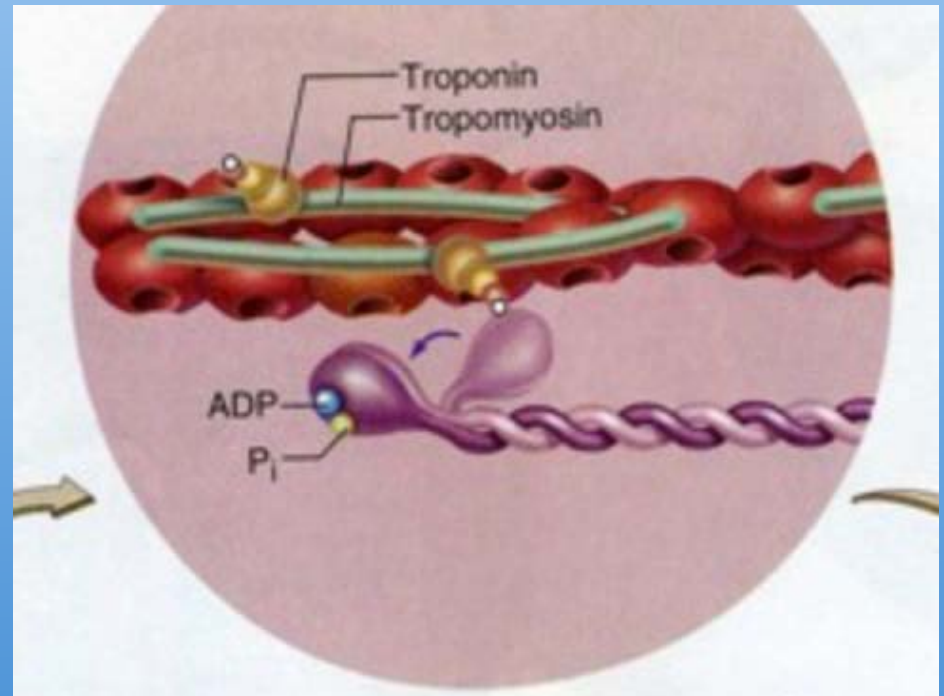
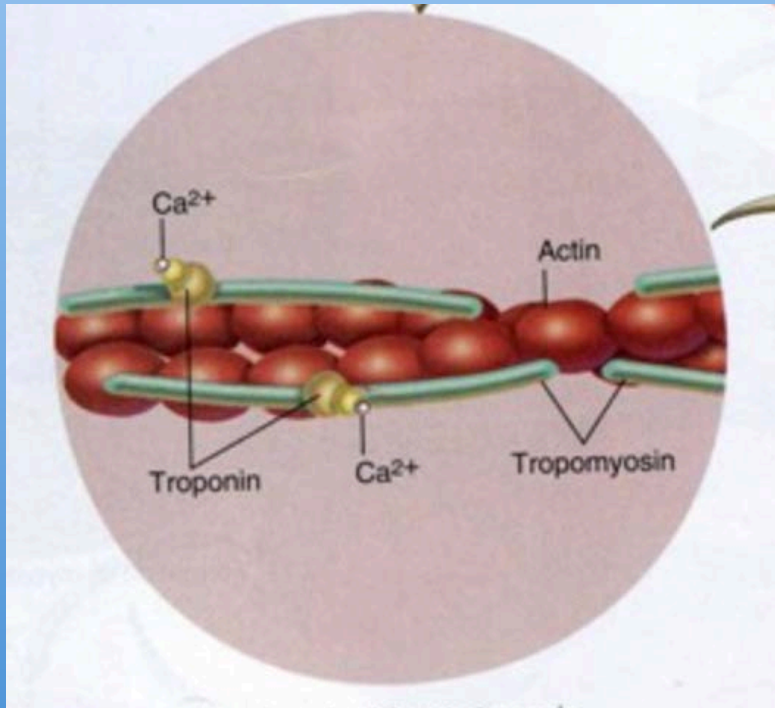


**Myosin molecules are bundled together to form thick filaments in skeletal muscles. A myosin molecule has two heads which can move forward and backward and binds to ATP molecule and an actin binding site. This flexible movement of head provides power stroke for muscle contraction.**





**The thin filaments are composed of three molecules - actin, tropomyosin and troponin. Actin is composed of actin subunits, joined together and twisted in a double helical chain. Each actin subunit has a specific binding site to which myosin head binds. Tropomyosin entwines around the actin. This cover the binding sites of actin subunits, preventing myosin heads from binding to them in an unstimulated muscle. Troponin molecules are attached to tropomyosin strands and facilitate tropomyosin movement so that myosin heads can bind to the exposed actin binding sites.**





**Muscle is the tissue that gives action to animals. Contraction, the power stroke of muscle, is the activity most often discussed: actin and myosin, tropomyosin and troponin and their coordinated interaction in the sarcomere.**

**There's another phase of cardiac and skeletal muscle activity, however, that is as important to muscle function as night is to day.**



**Repetitive muscle activity requires not only repetitive *contraction*, but also repetitive *relaxation* - it's a two-stroke cycle**

**Interference with the dynamics of diastolic relaxation can have an effect similar to weakening of systolic contraction: increased filling pressures of the left atrium result in elevated pulmonary venous pressure**



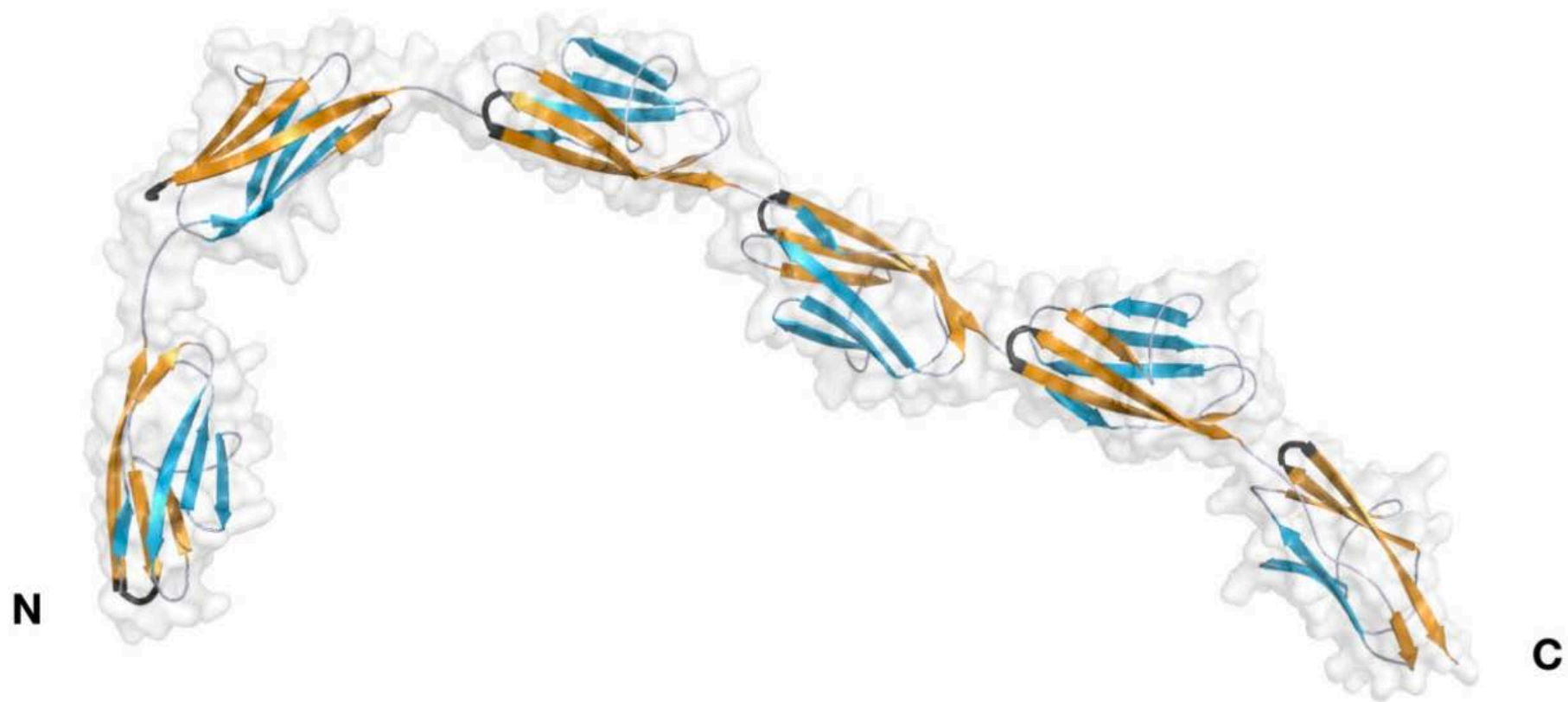
***Titin* is the largest known protein. Human cardiac titin has over 38,000 amino acids in its primary structure.**

**By comparison, serum albumin has 585 amino acids and apoB (the large protein of VLDL and LDL cholesterol-transport particles) has 4500 amino acids.**

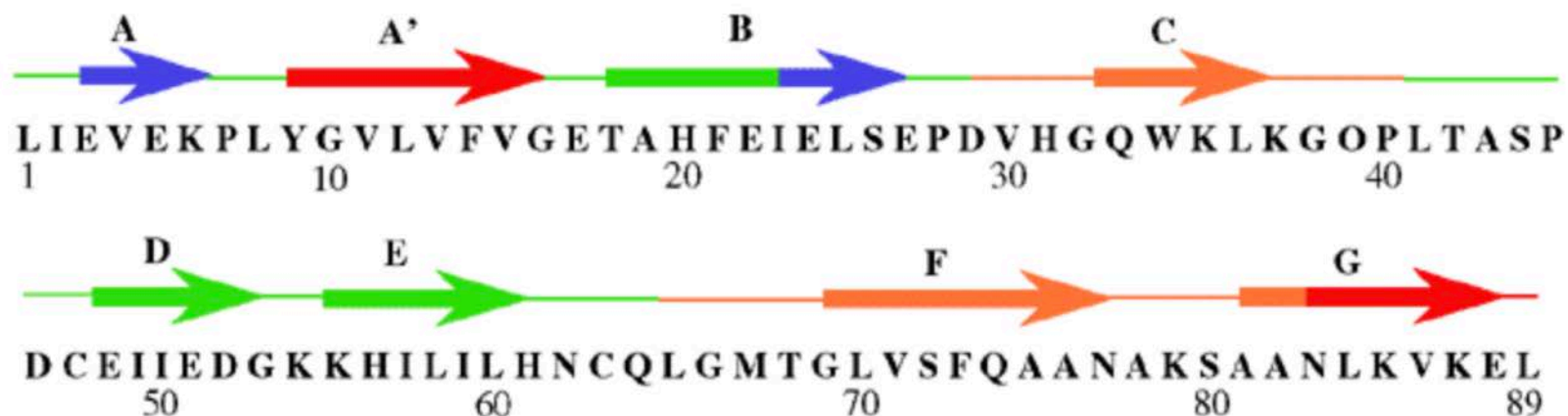
**ApoA1, the primary apolipoprotein of HDL, has 245 amino acids.**

**Titin serves to organize contractile elements of the myocardial sarcomere and determines how easily the cell will stretch in response to a given pressure/tension load.**

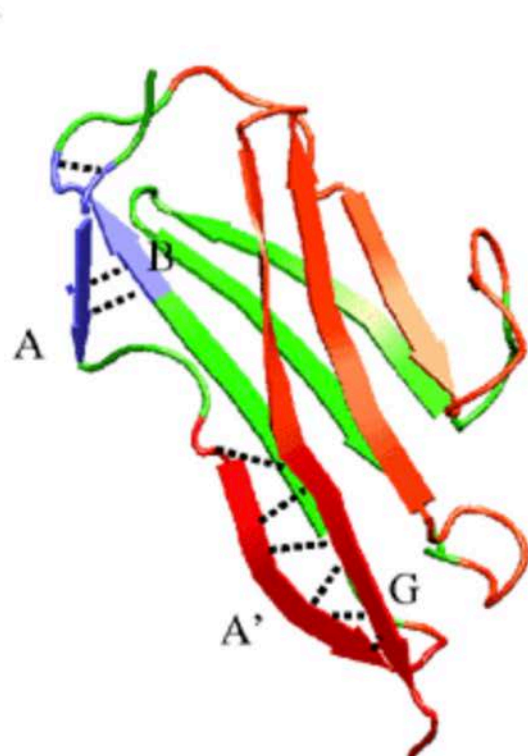




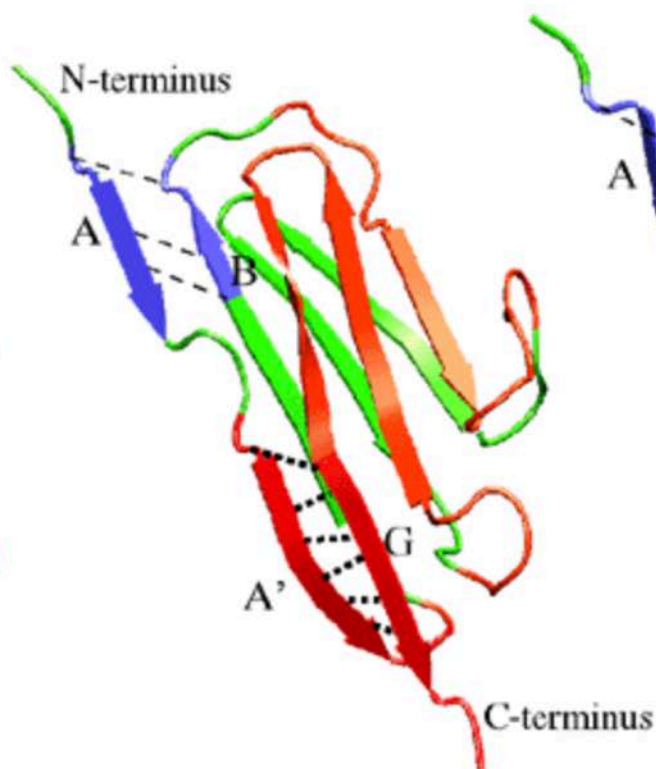




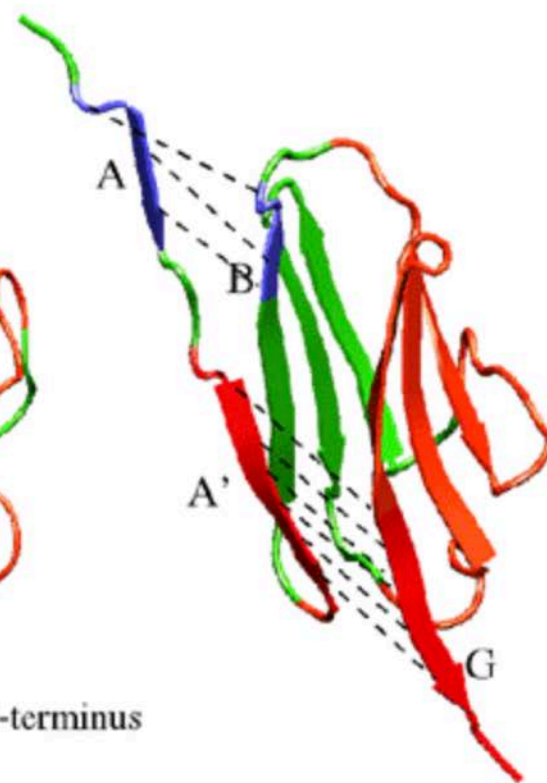
(a) sequence and secondary structure



(b) native structure

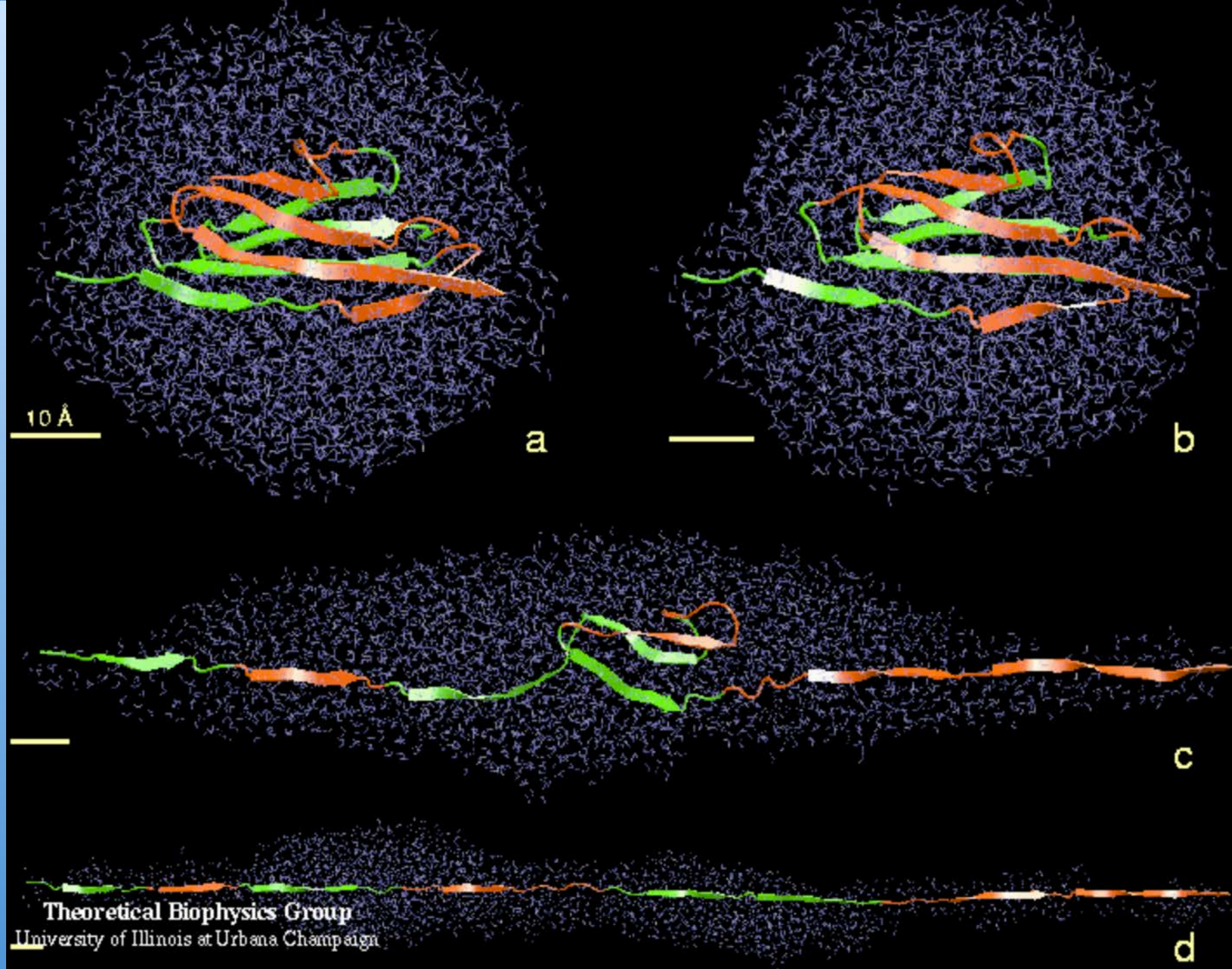


(c) extension of 10 Å



(d) extension of 25 Å

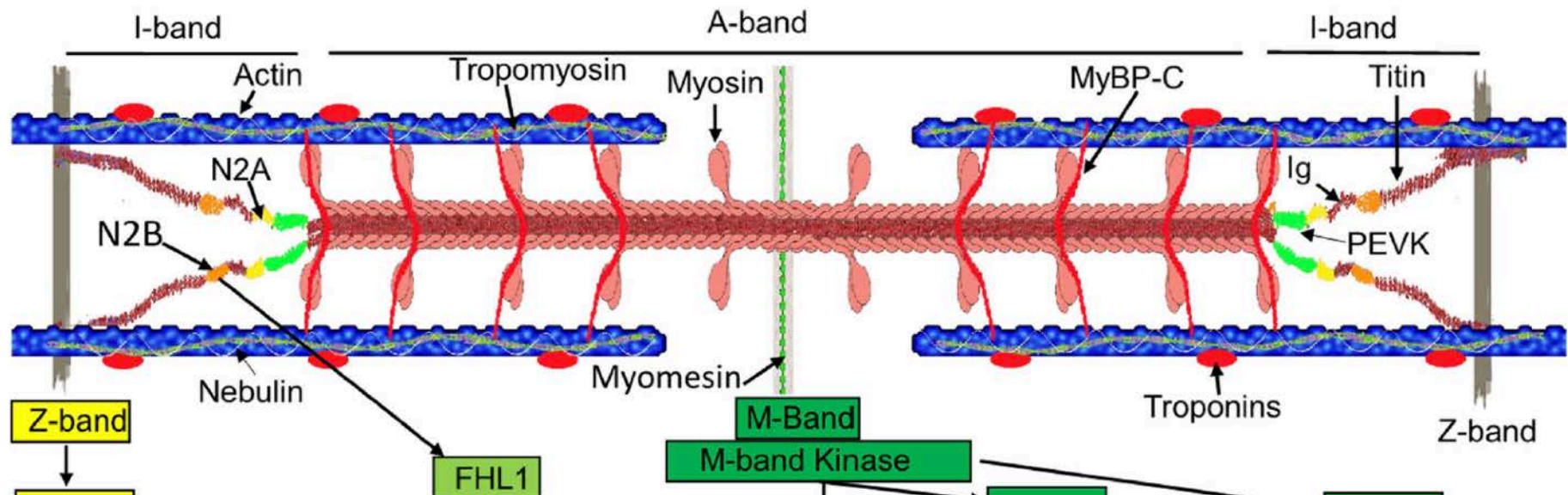




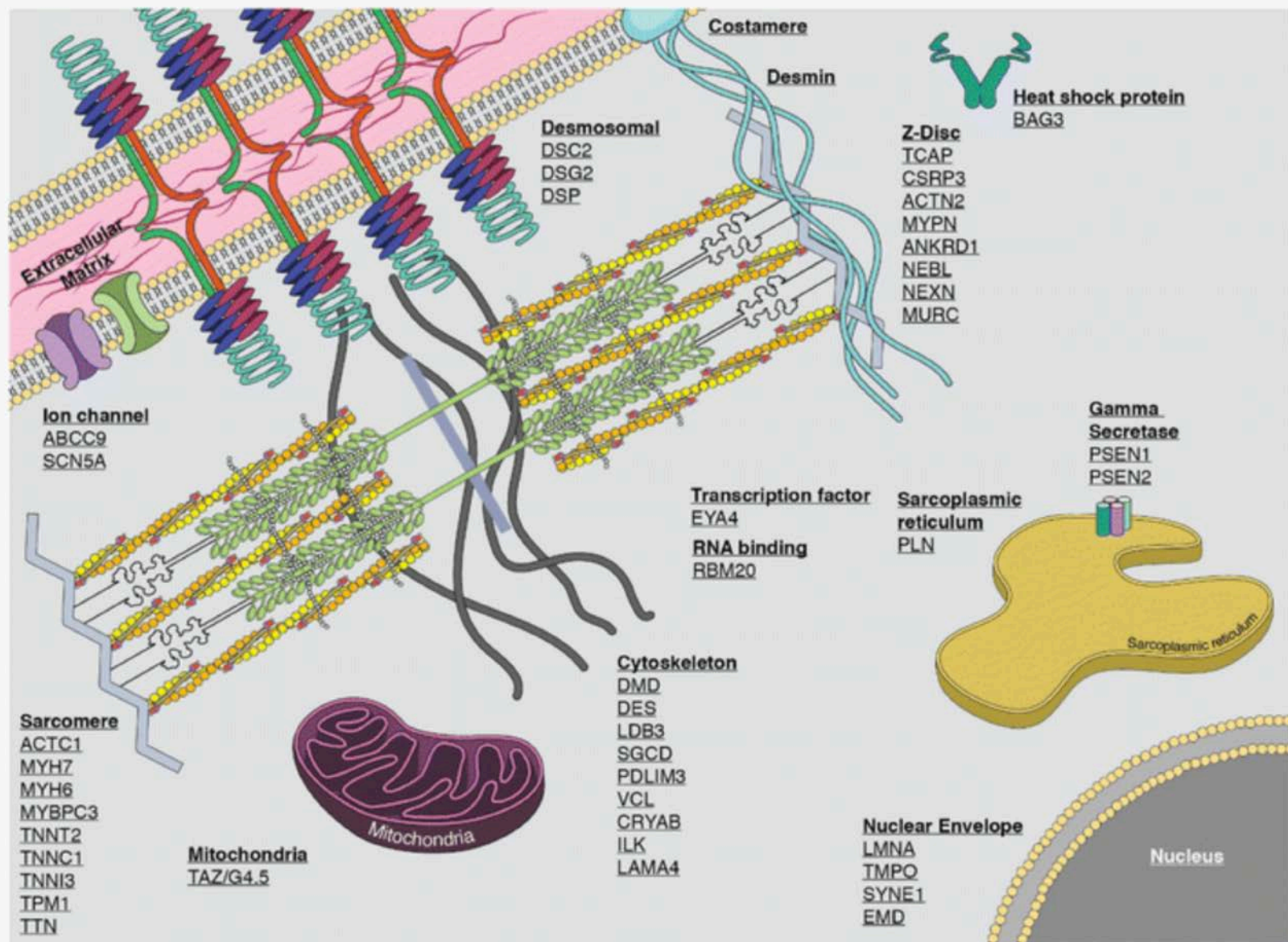


**Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation.**







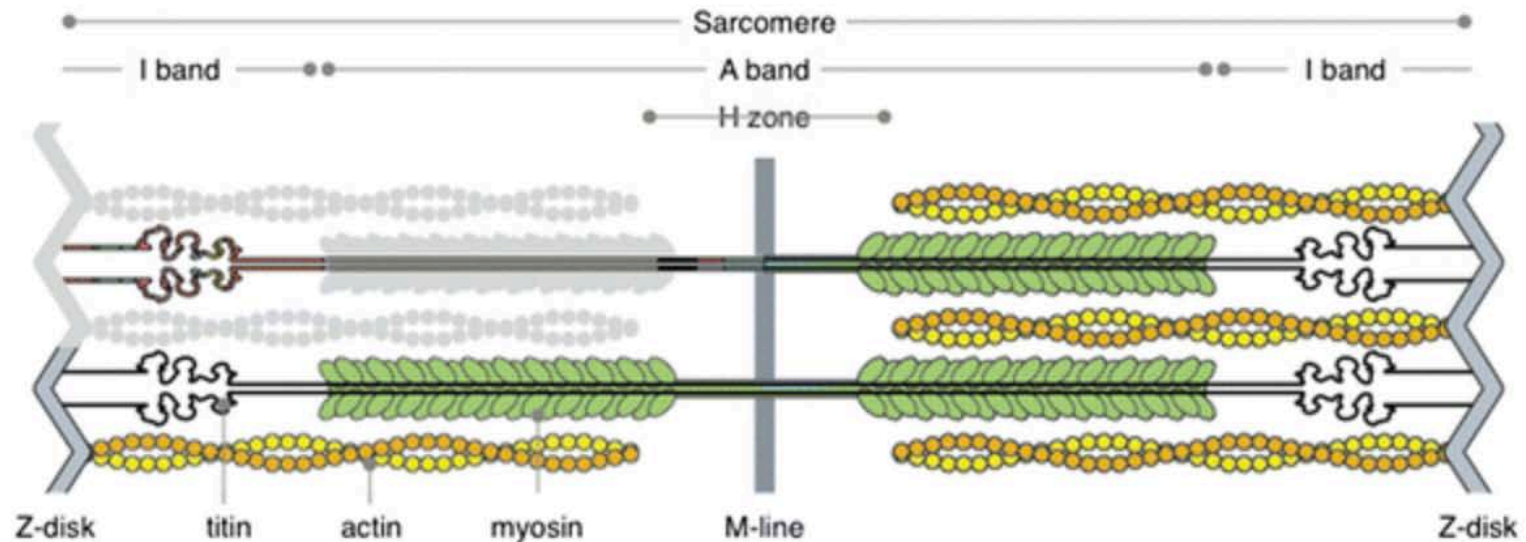


**Fig. 4**

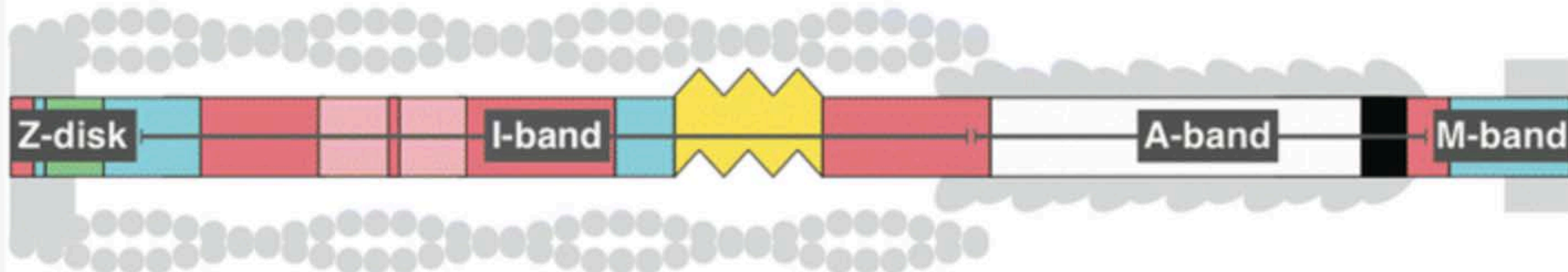
Schematic section of cardiomyocyte depicting genes associated with non-syndromic familial DCM (Hershberger et al. [2013](#)). Sarcomeric gene **TTN** is the major DCM gene, accounting for 25% of familial DCM cases



## a Sarcomere structure



## b Domains within titin protein



Unique sequences

Immunoglobulin-like domain

Z-repeats

Alternative splicing

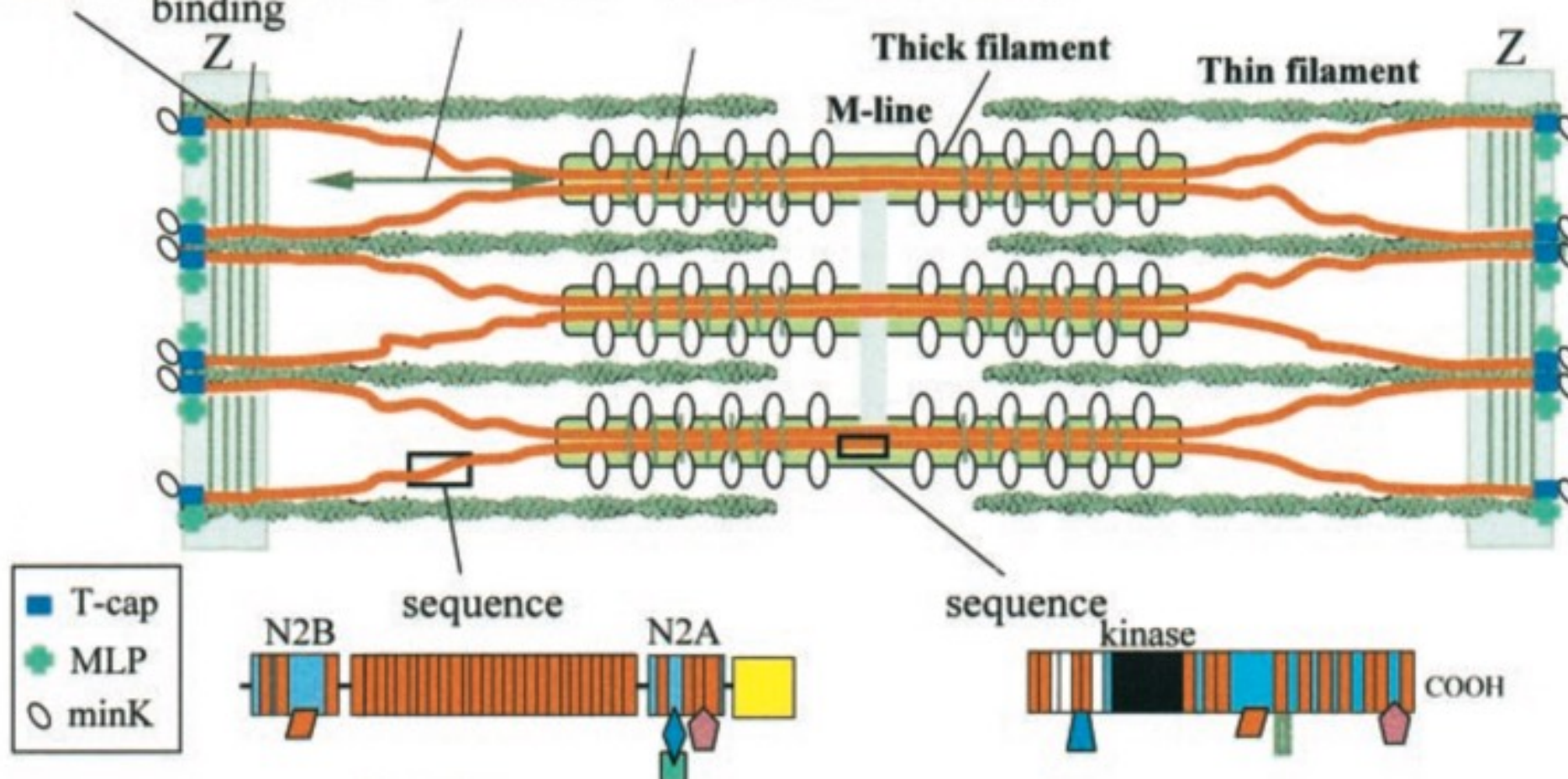
PEVK-rich sequence

Fibronectin type 3-like domain

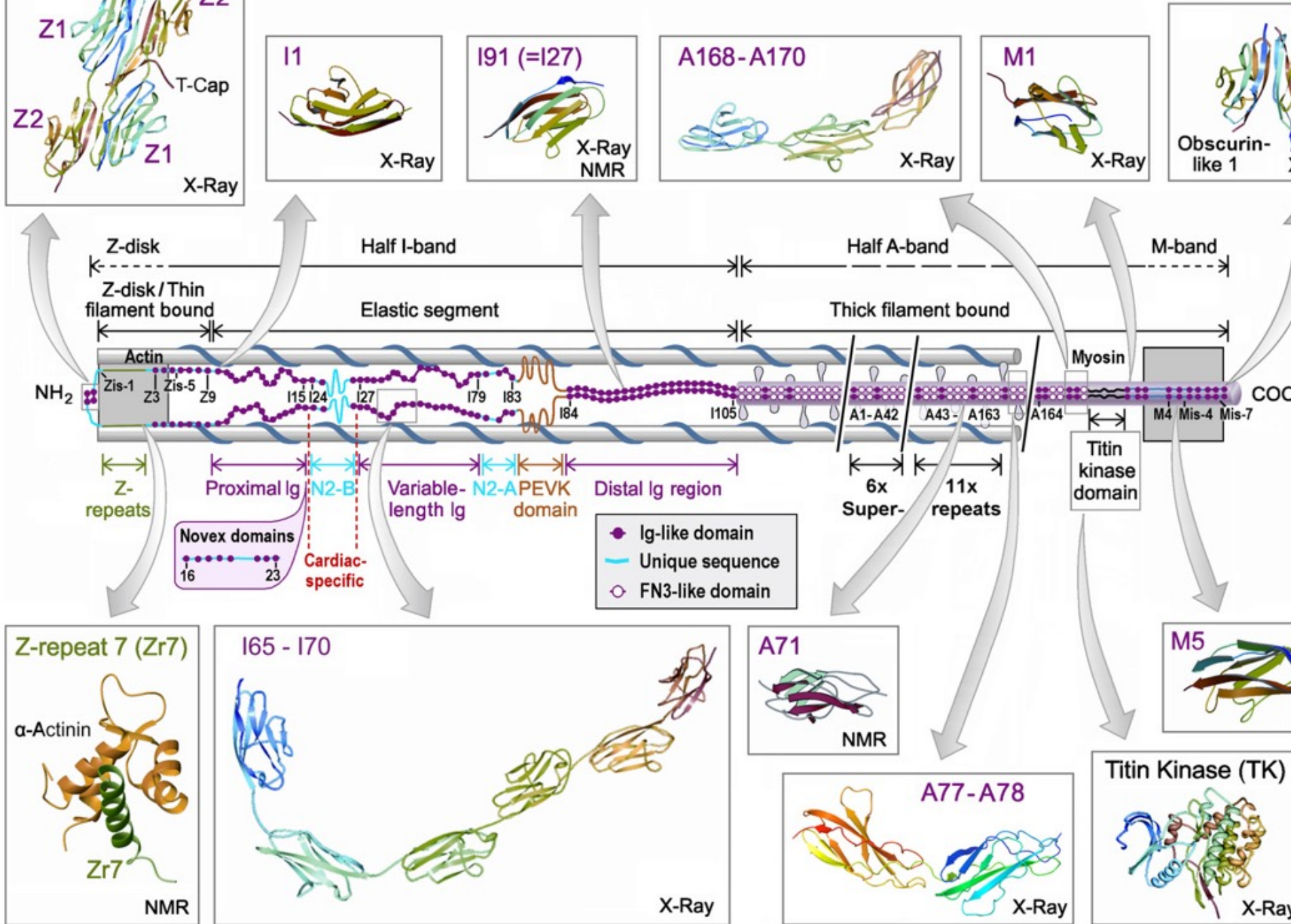
Titin kinase domain



**TITIN:** thin-filament binding      extensible      thick-filament binding

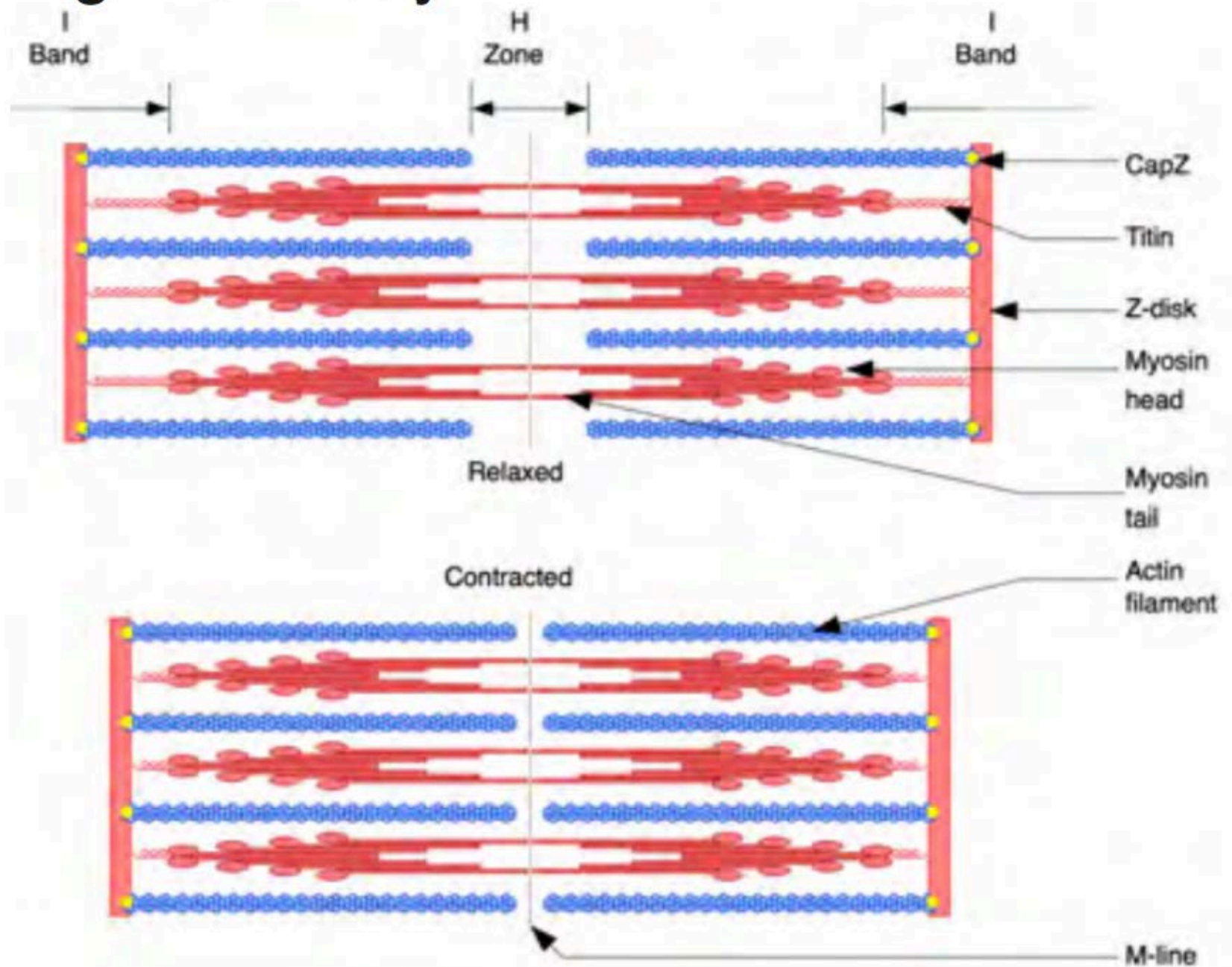






**FIGURE 1. Layout of titin in the half-sarcomere and atomic structures of titin domains available to date.** Shown are two strands of the cardiac N2BA titin i. Atomic structures were obtained from the Protein Data Bank: for original references, see the text. X-Ray indicates that the structure was resolved by x-ray crystallography.

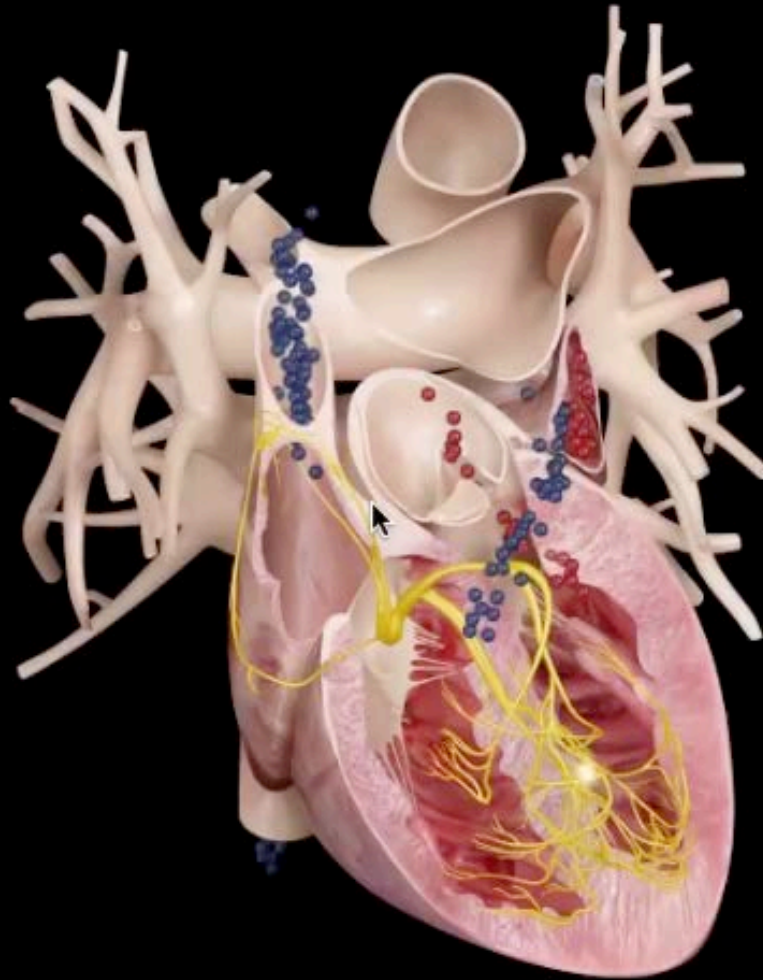






**Heart failure (HF) is a complex clinical syndrome which concerns the impaired ability of the heart to pump and/or fill with blood, resulting in inadequate cardiac output to meet metabolic demands or, more commonly, adequate cardiac output but only due to compensatory neurohormonal activation.**





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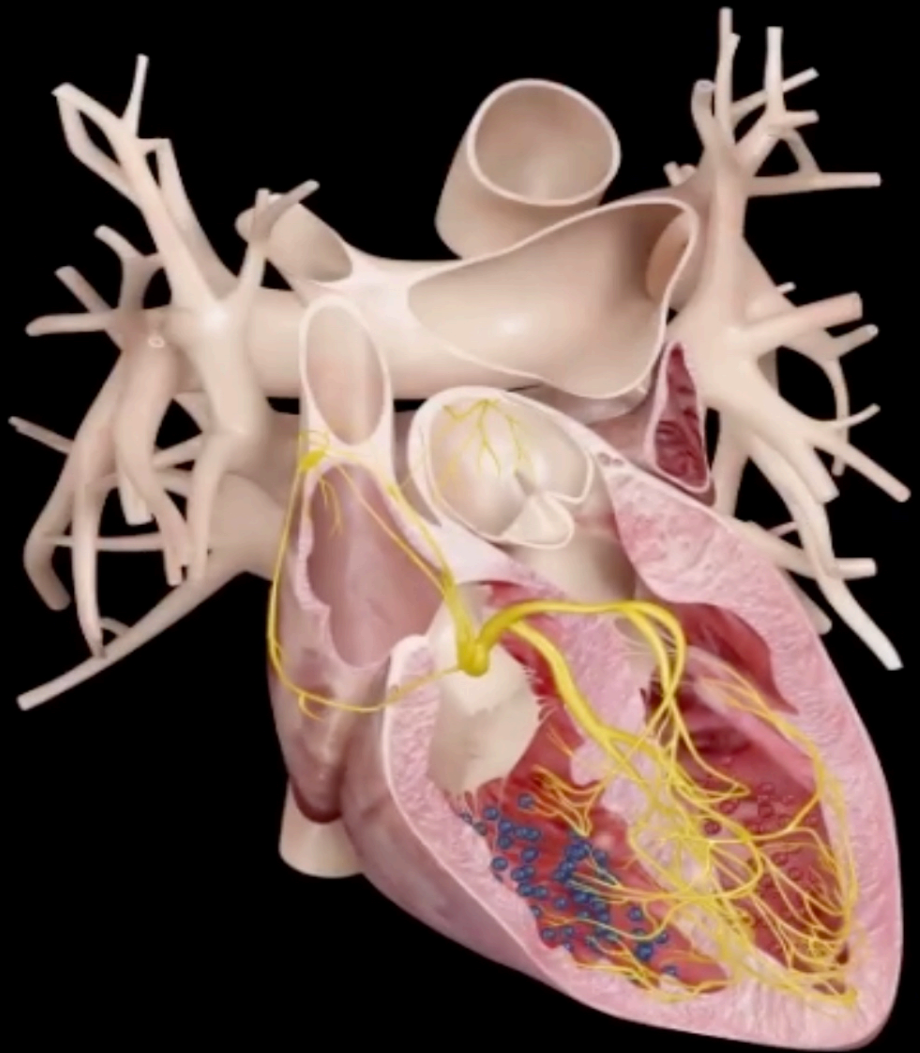
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**VF**



REVIEW

## RBM20, a potential target for treatment of cardiomyopathy via titin isoform switching

Wei Guo<sup>1,2</sup>  • Mingming Sun<sup>1,2</sup>

REVIEW

## Obscurin variants and inherited cardiomyopathies

Steven Marston<sup>1</sup>

Journal of Muscle Research and Cell Motility (2005) 26:389–400  
DOI 10.1007/s10974-005-9021-x

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## Functional properties of the titin/connectin-associated proteins, the muscle-specific RING finger proteins (MURFs), in striated muscle

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EDITORIAL

## Special issue on titin and its binding proteins in striated muscle

Amy Li<sup>1,2</sup> • Cristobal dos Remedios<sup>1</sup>







































































