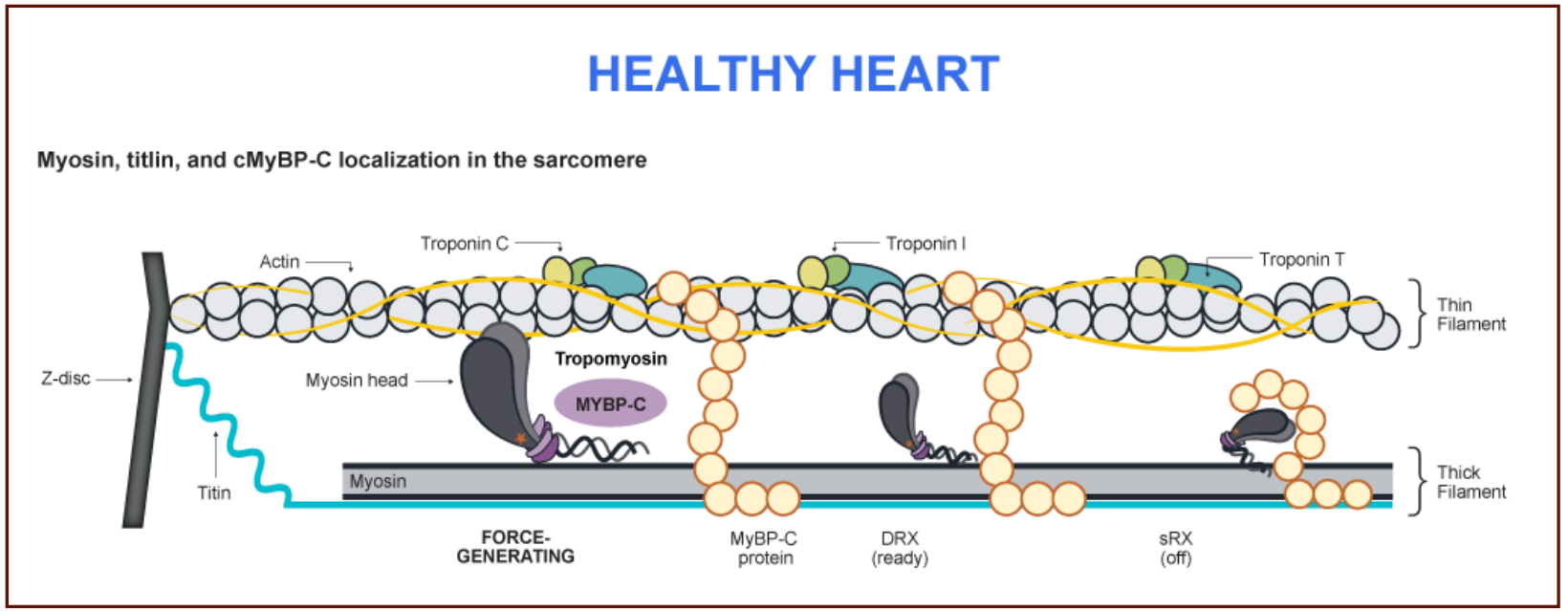
MYBPC3 – the MASTER protein

MYBPC3 is the MASTER protein because it …

- Regulates the timing and magnitude of each contraction in the sarcomere
- Modulates the force and speed of each contraction
- Accounts for ~1/3 of the total sarcomere protein content

Three main governing actions

1. Governs force by controlling myosin head availability through differential binding of myosin and actin
2. Governs activation through thin filament sensitization to myosin at low calcium levels
3. Governs tension by controlling sarcomere length through titin elongation



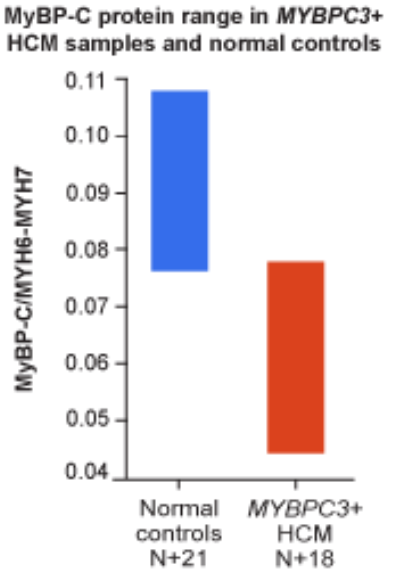
cMyBP-C: cardiac myosin binding protein-C; *MYBPC3:* myosin binding protein C3.

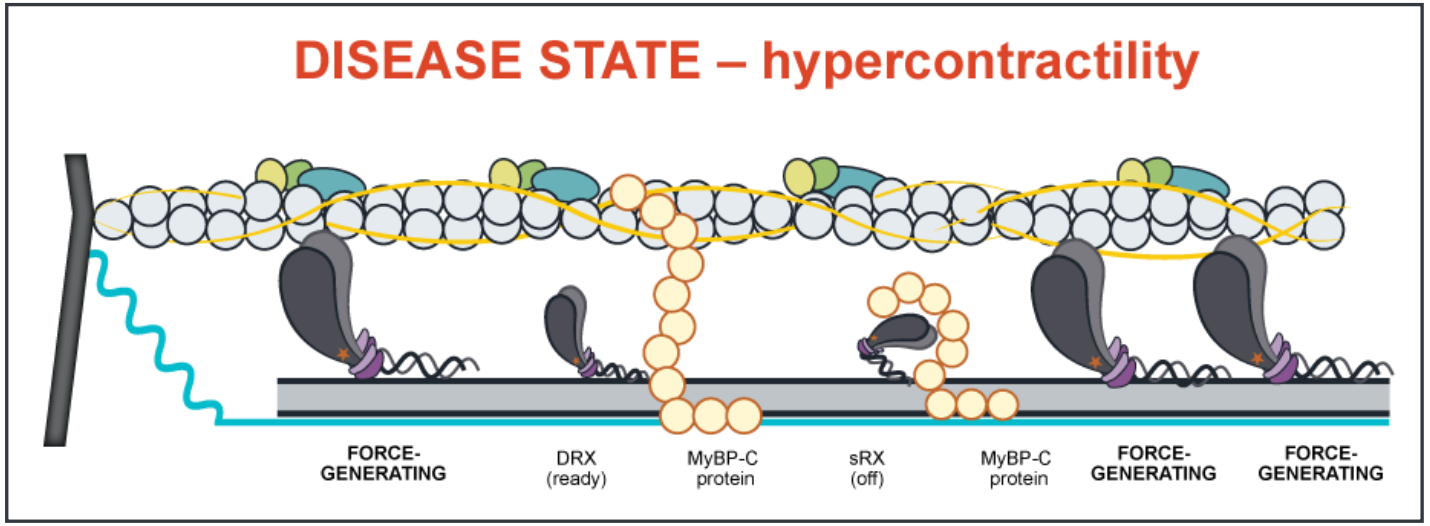
Arts et al., *J Mol Cell Cardiol*. 2024;190:13–23; Bennet et al., *Circ Res*. 2025;137(9):1226–1228; Heling et al., *J Muscle Res Cell Motil*. 2020;41(1):91–101; McNamara et al., *PLoS One*. 2017;12(6):e0180064; O'Leary et al., *J Mol Cell Cardiol*. 2019;127:165–173; Suay-Corredera et al., *FEBS Lett*. 2022;596(6):703–746.

MYBPC3 and sarcomeric function

Normal heart:	HCM heart:
Force-generating stage	
Normally 10% of myosin heads in the force-generating stage	More myosin heads are engaged with actin due to deficit in MyBP-C proteins
Disordered relaxed stage (DRX: ready)	
Normally 45% of myosin heads in the DRX stage	More myosin heads are in the DRX stage and available for force generation
Super relaxed stage (SRX: off)	
Normally 45% of myosin heads in the SRX stage	Fewer MyBP-C proteins available to keep myosin heads contracted in the SRX stage inhibiting diastole

MYBPC3 **mutations result in insufficient MyBP-C protein levels**





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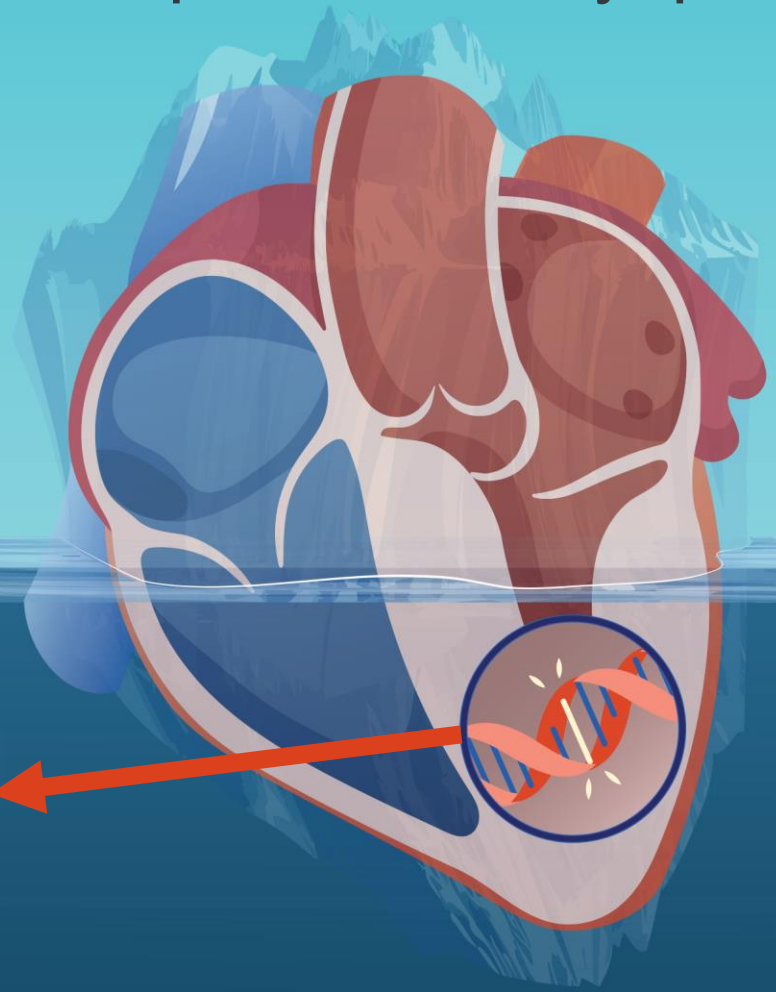
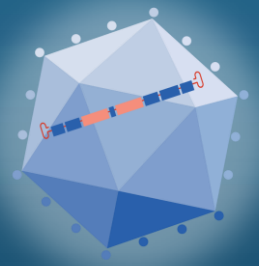
TN-201 gene replacement therapy in *MYBPC3*-associated hypertrophic cardiomyopathy

Pathogenic variants in the *MYBPC3* gene results in protein insufficiency which leads to myocardial disarray and results in hypercontractility and excessive energy consumption during every heartbeat, ultimately leading to hypertrophy



Gene replacement therapy delivers TN-201



TN-201 HCM gene replacement therapy is delivered in a single intravenous dose with the potential for a long-lasting response. Potential treatment effects of gene therapy are:

WHAT WE CAN SEE

- **Ameliorate complications**
- **Decrease symptoms**

WHAT WE CAN'T SEE

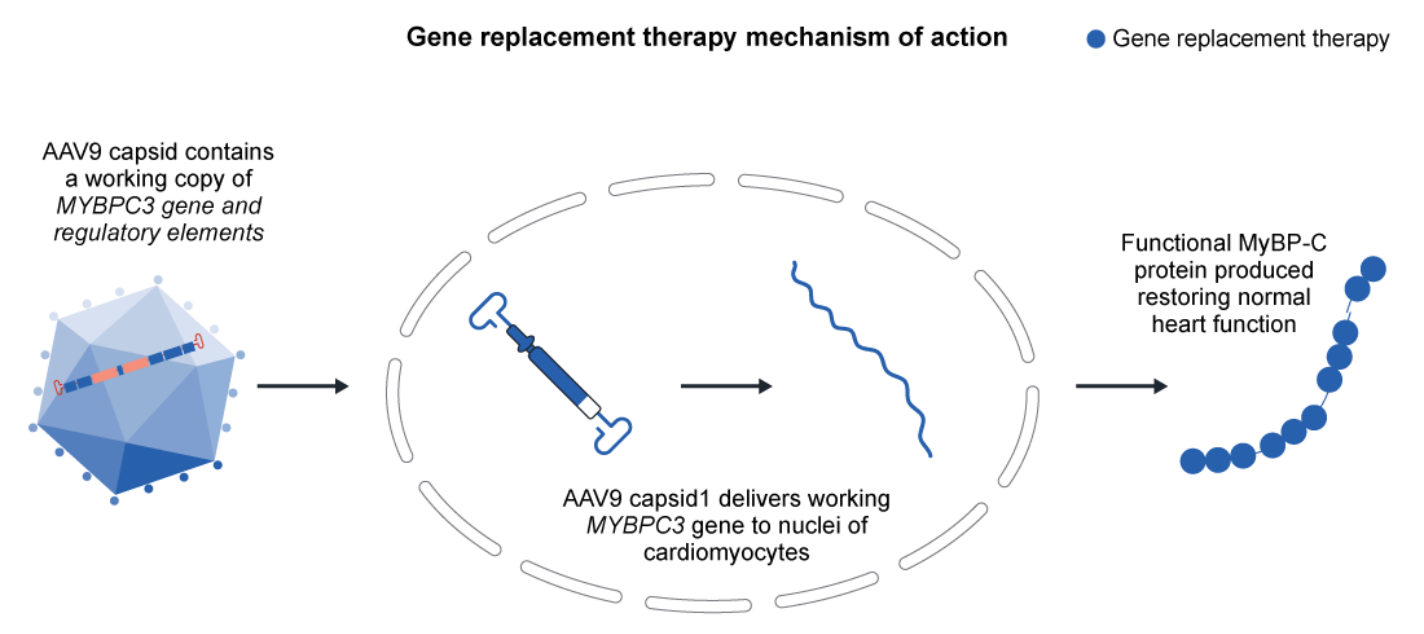
- **Address disease mechanism**
- **Halt disease progression**
- **Target etiology**

TN-201 gene replacement therapy is designed to deliver a functional copy of *MYBPC3* gene into the cardiomyocyte with the potential to slow or even reverse the course of the disease

Note: TN-201 is in clinical testing and has not been approved by the FDA or any other regulatory authority.

MYBPC3: myosin binding protein C3. Desai et al., *Cardiovasc Res*. 2025;121(17):2628–2631: Greer-Short et al., *Nat Commun*. 2025;16(1):2196.

Restoration of MyBP-C protein and normal heart function



Cardiac function	*MYBPC3*-HCM heart	TN201 gene therapy desired effect
Energetic Function	↑	↓
Cross-bridge cycling kinetics	↑	↓
Diastolic filling time	↓	↑
Cardiac perfusion	↓	↑
Blood flow	↓	↑
Stroke volume	↓	↑
Left ventricle compliance	↓	↑

Treatment with gene replacement therapy potentially restores MyBP-C protein and the normal physiological regulation of sarcomeres. This allows muscle contractility and relaxation, under normal conditions and under conditions of increased demand, e.g., exercise or stress

Treatment with TN-201 gene replacement therapy potentially restores normal heart function

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