Servizo de Cardioloxía

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Understanding the etiology of HCM and pathways for intervention

Roberto Barriales Villa, MD, PhD, FESC

Unidad de Cardiopatías Familiares

Complexo Hospitalario Universitario A Coruña, Spain

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UNIVERSIDADE DA CORUÑA

inibic instituto de investigación biomédica de a coruña

MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

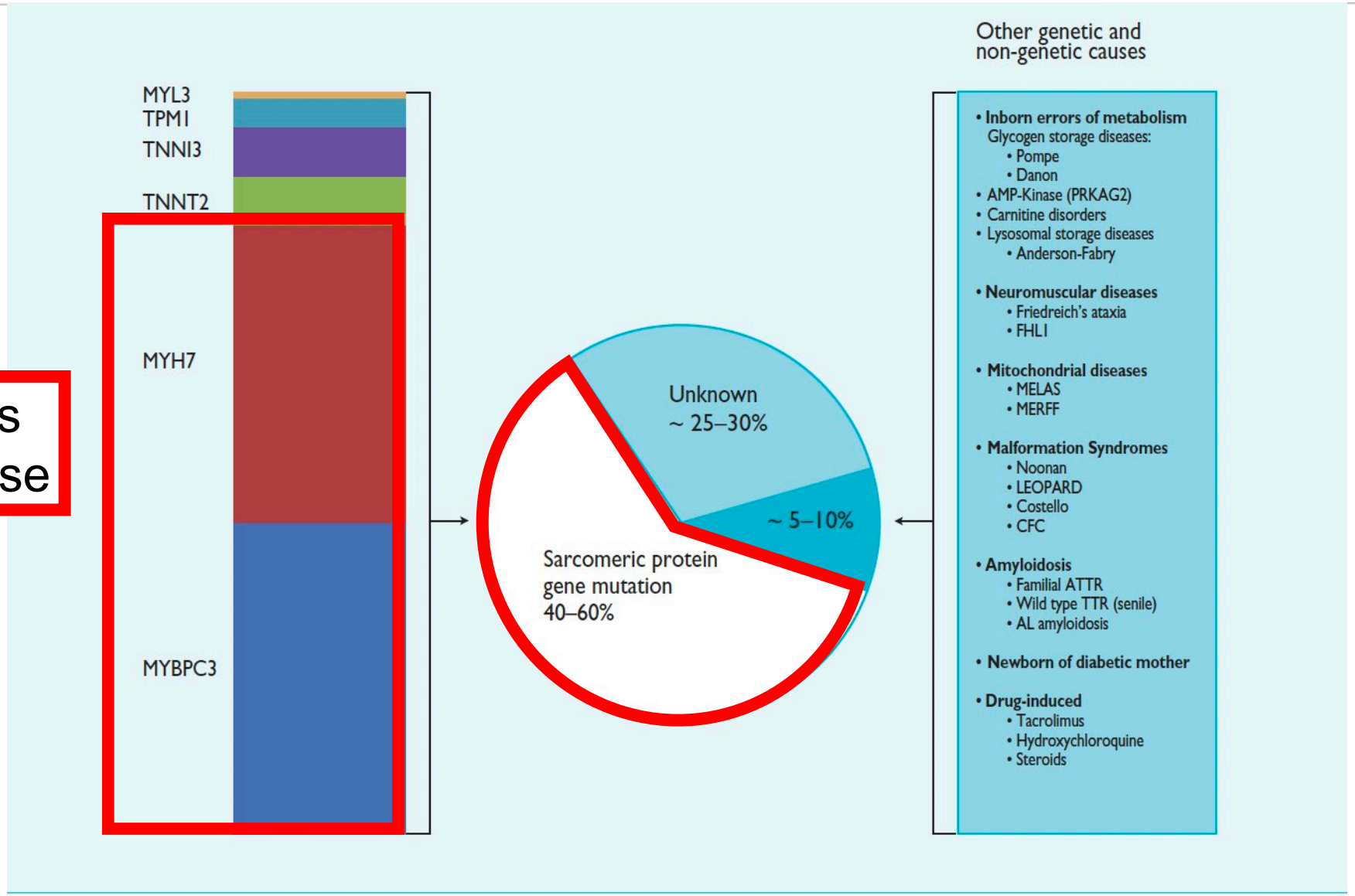
ciber | CV CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Enfermedades Cardiovasculares

DISCLOSURES

-Grants: BMS, Sanofi, Healthincode
-Advisory Board: BMS, Sanofi, Amicus, Pfizer, Alnylam, Cytokinetics

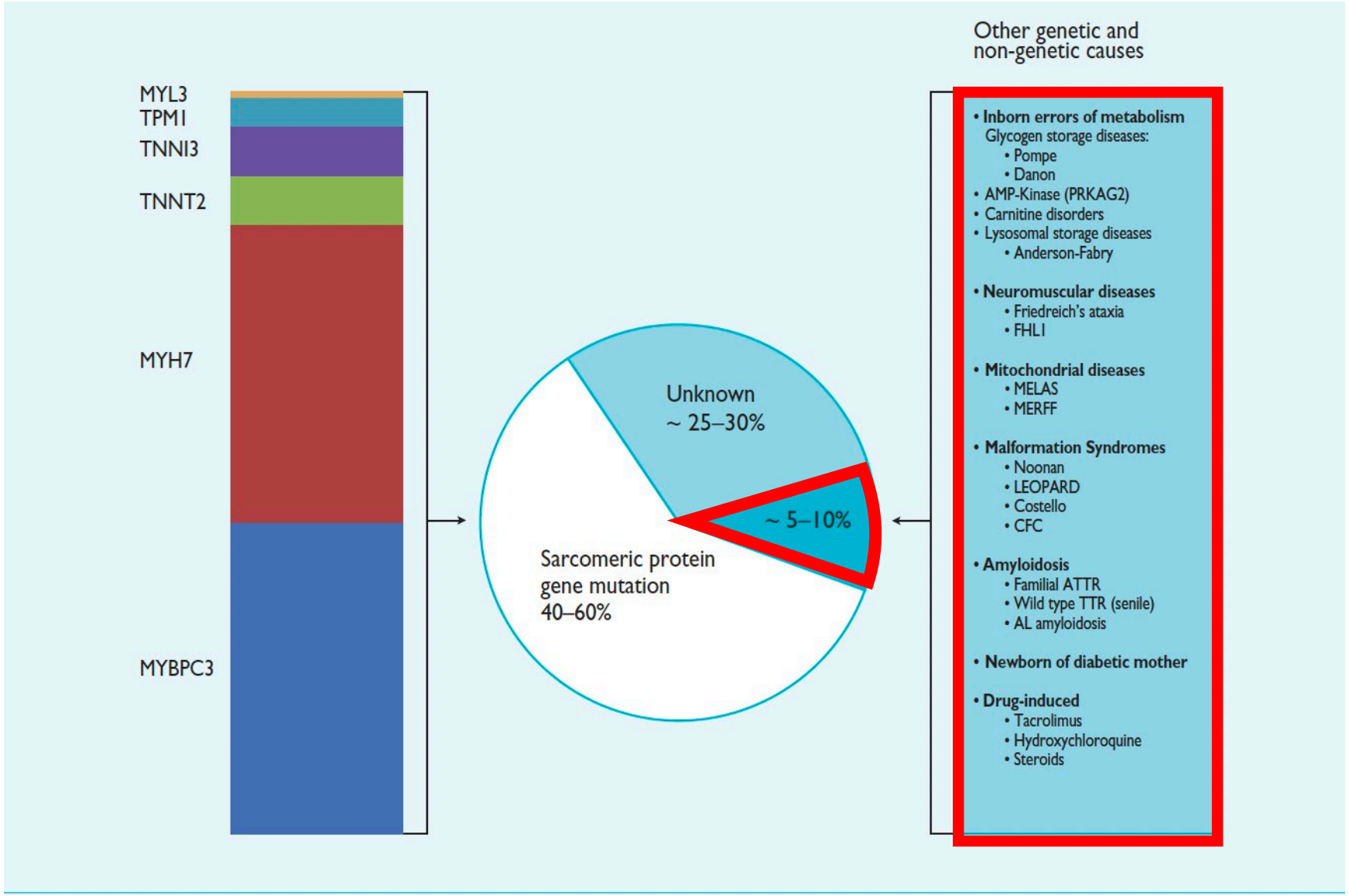
Disease of sarcomeric proteins

- ✓ Young patients
- ✓ Familial disease



Elliott P et al. 2014 ESC HCM Guidelines

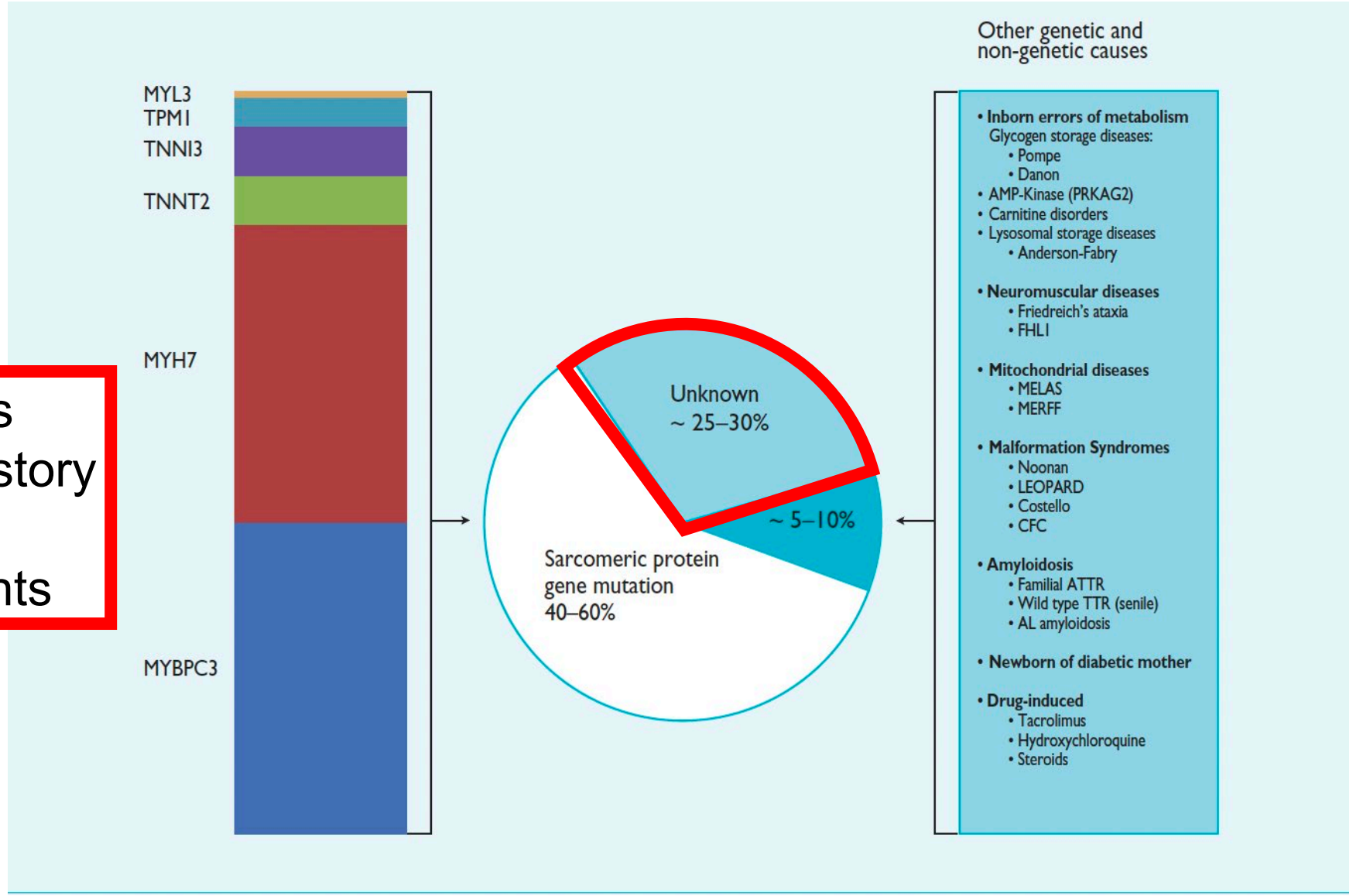
Inherited Metabolic/NM diseases



Elliott P et al. 2014 ESC HCM Guidelines

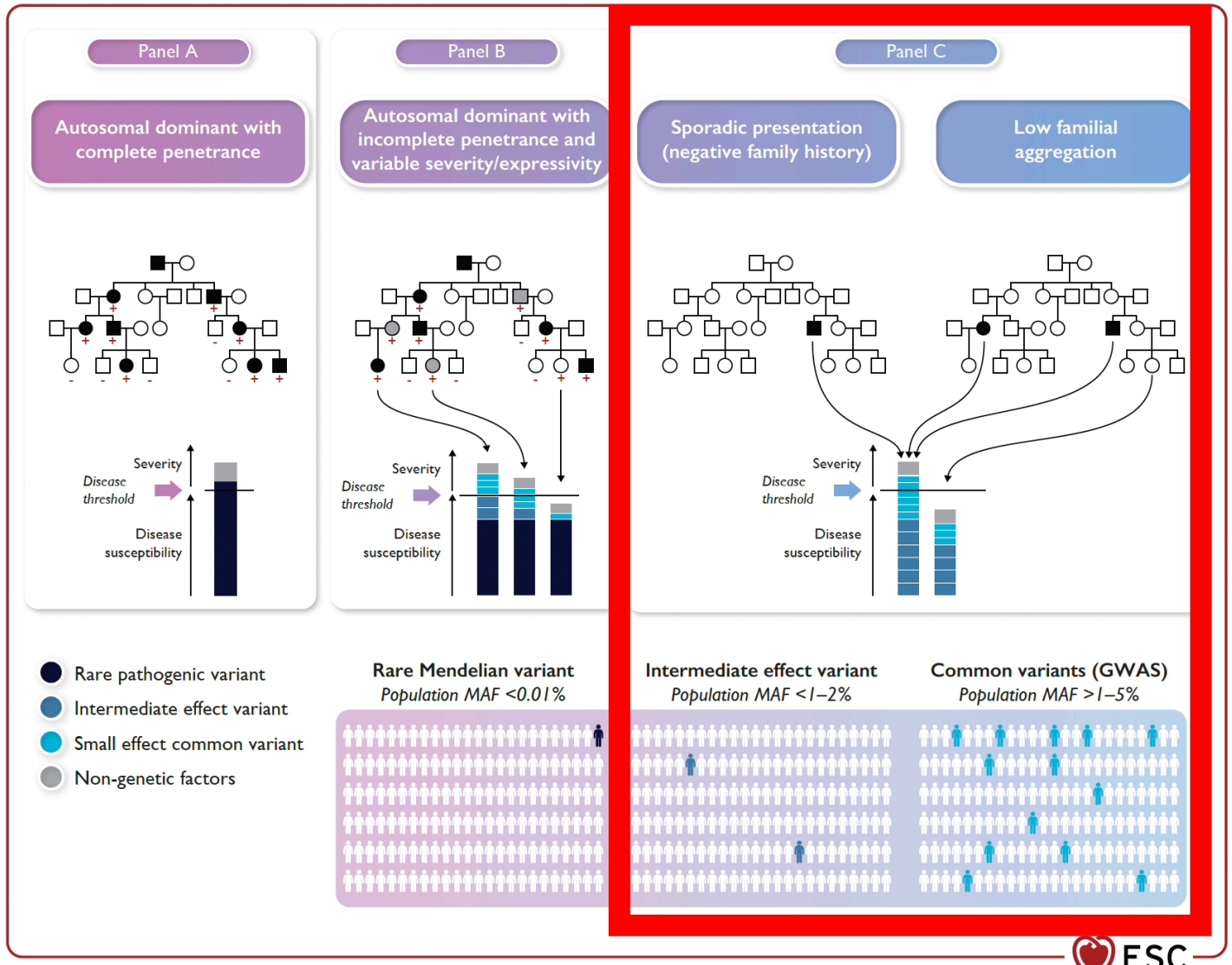
No monogenic variant-Complex etiology

- ✓ Older patients
- ✓ No familial history
- ✓ HTA
- ✓ Less CV events



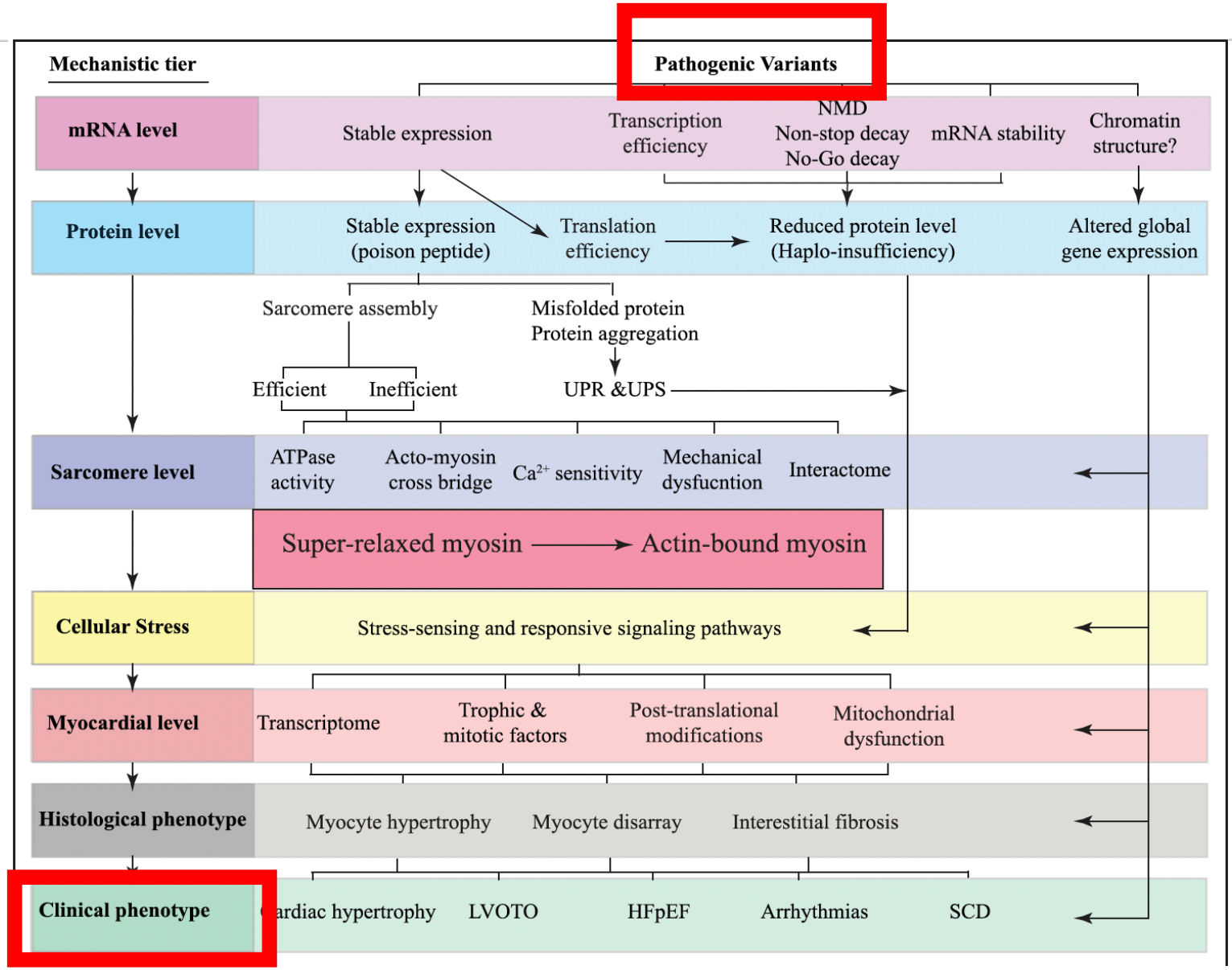
Elliott P et al. 2014 ESC HCM Guidelines

Complex Etiology: Polygenic Inheritance



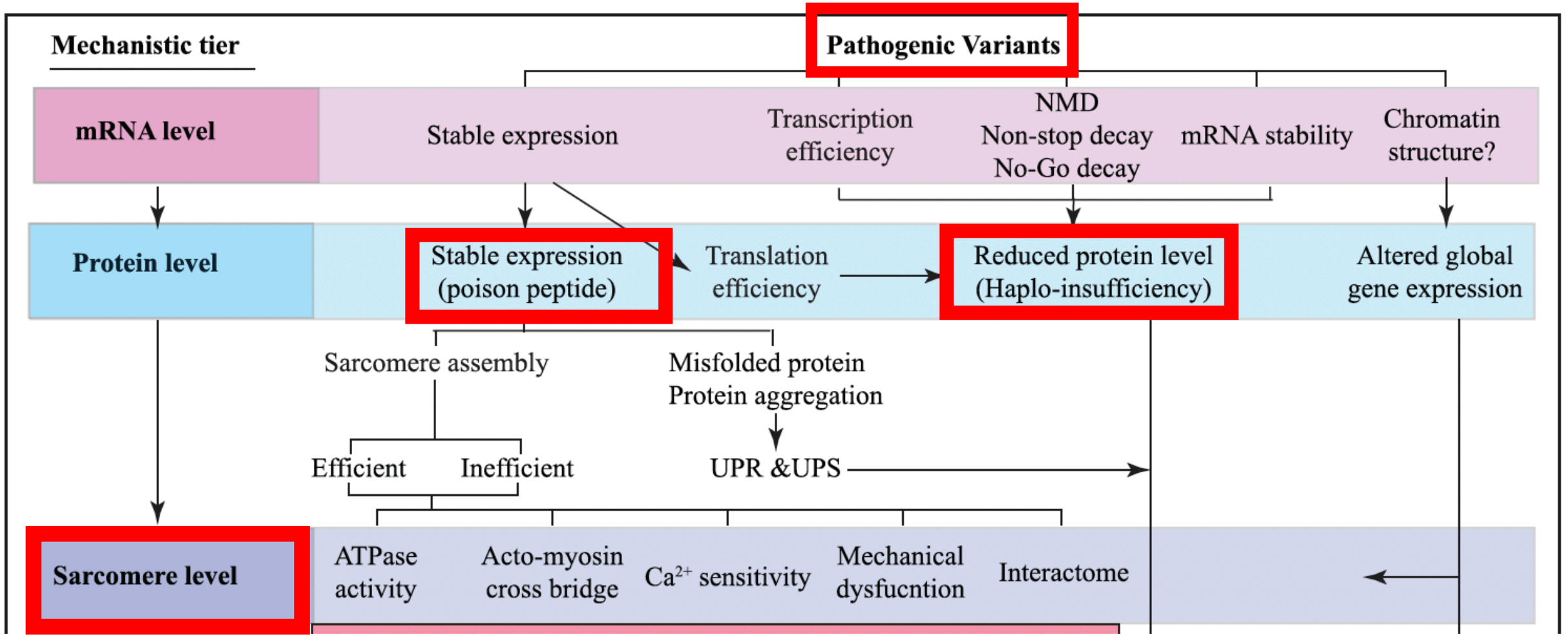
Arbelo E et al. 2023 ESC Cardiomyopathies Guidelines

Sarcomeric variant to phenotype……



Marian AJ. Circulation Research. 2021;128:1533–1553

Sarcomeric variant to phenotype……



Marian AJ. Circulation Research. 2021;128:1533–1553

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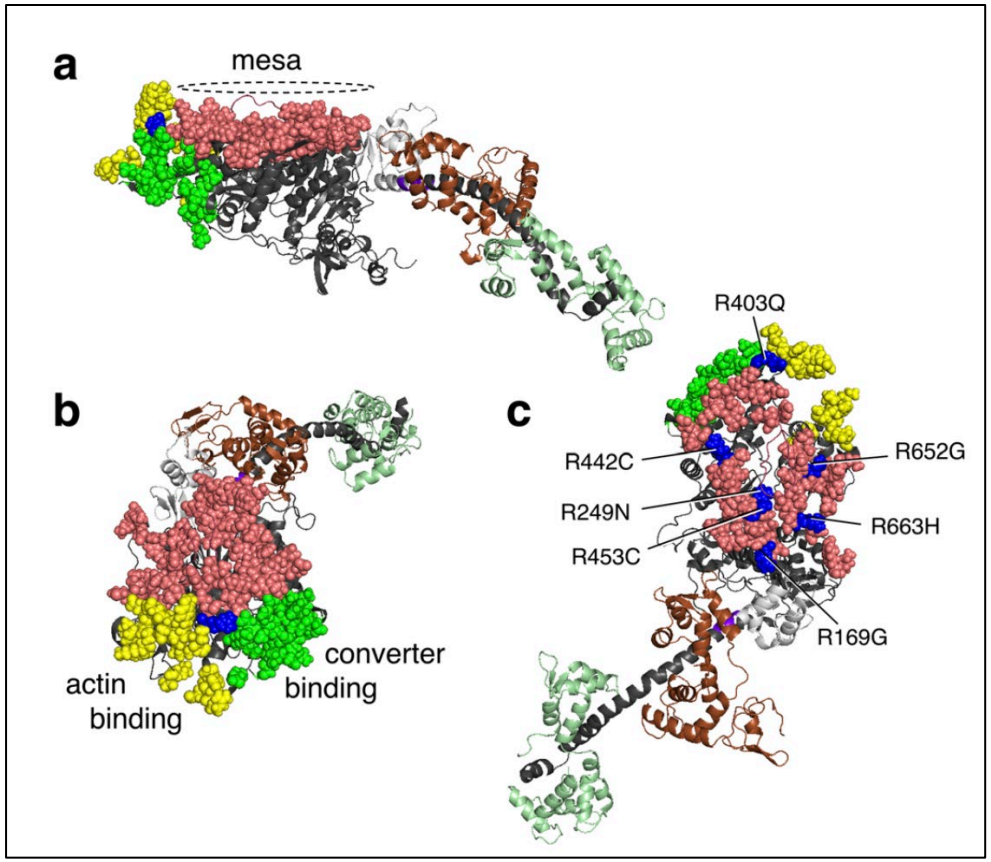
MYH7 mutations induce sarcomere **hypercontractility**



SCIENCE ADVANCES | RESEARCH ARTICLE

BIOCHEMISTRY

The hypertrophic cardiomyopathy mutations R403Q and R663H increase the number of myosin heads available to interact with actin

Saswata S. Sarkar[1,2]*, Darshan V. Trivedi[1,2]*, Makenna M. Morck[1,2]*, Arjun S. Adhikari[1,2], Shaik N. Pasha[3], Kathleen M. Ruppel[1,2,4†], James A. Spudich[1,2†]

Hypertrophic cardiomyopathy β-cardiac myosin mutation (P710R) leads to hypercontractility by disrupting super relaxed state

Alison Schroer Vander Roest[a,b,c,d,1], Chao Liu[d,e,1], Makenna M. Morck[d,e], Kristina Bezold Kooiker[a,f], Gwanghyun Jung[a,d], Dan Song[d,e], Aminah Dawood[d,e], Arnav Jhingran[a], Gaspard Pardon[b,c,d], Sara Ranjbarvaziri[a,d], Giovanni Fajardo[a,d], Mingming Zhao[a,d], Kenneth S. Campbell[g,h], Beth L. Pruitt[b,c,d,i], James A. Spudich[d,e,2], Kathleen M. Ruppel[d,e], and Daniel Bernstein[a,d,2]

Trivedi DV et al. Biophys Rev 10, 747 27-48, (2018)
Sakar SS et al. Sci Adv 6 (2020)
Vander Roest AS et al. Proc Natl Acad Sci U S A 118 (2021)

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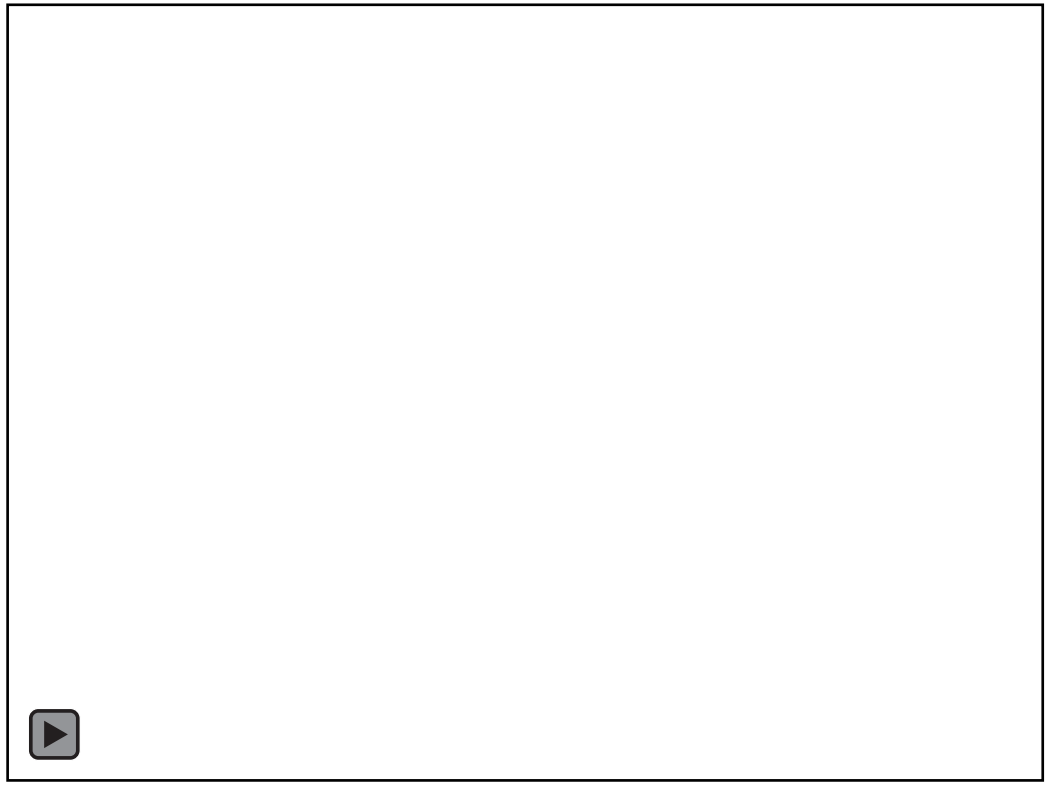
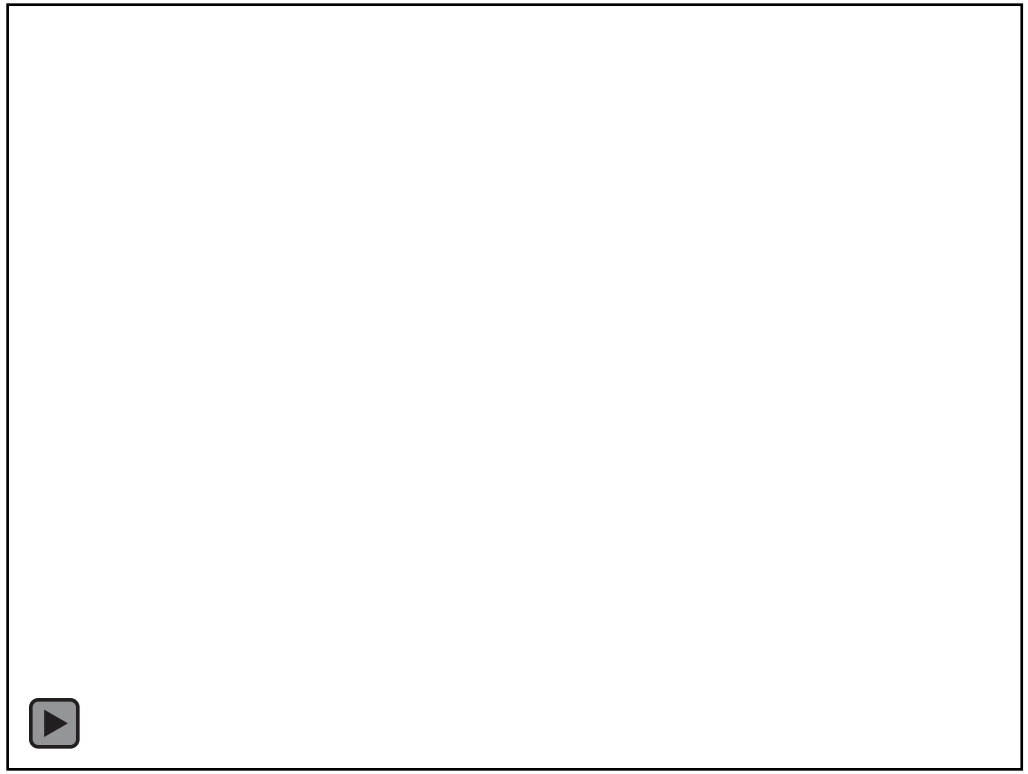
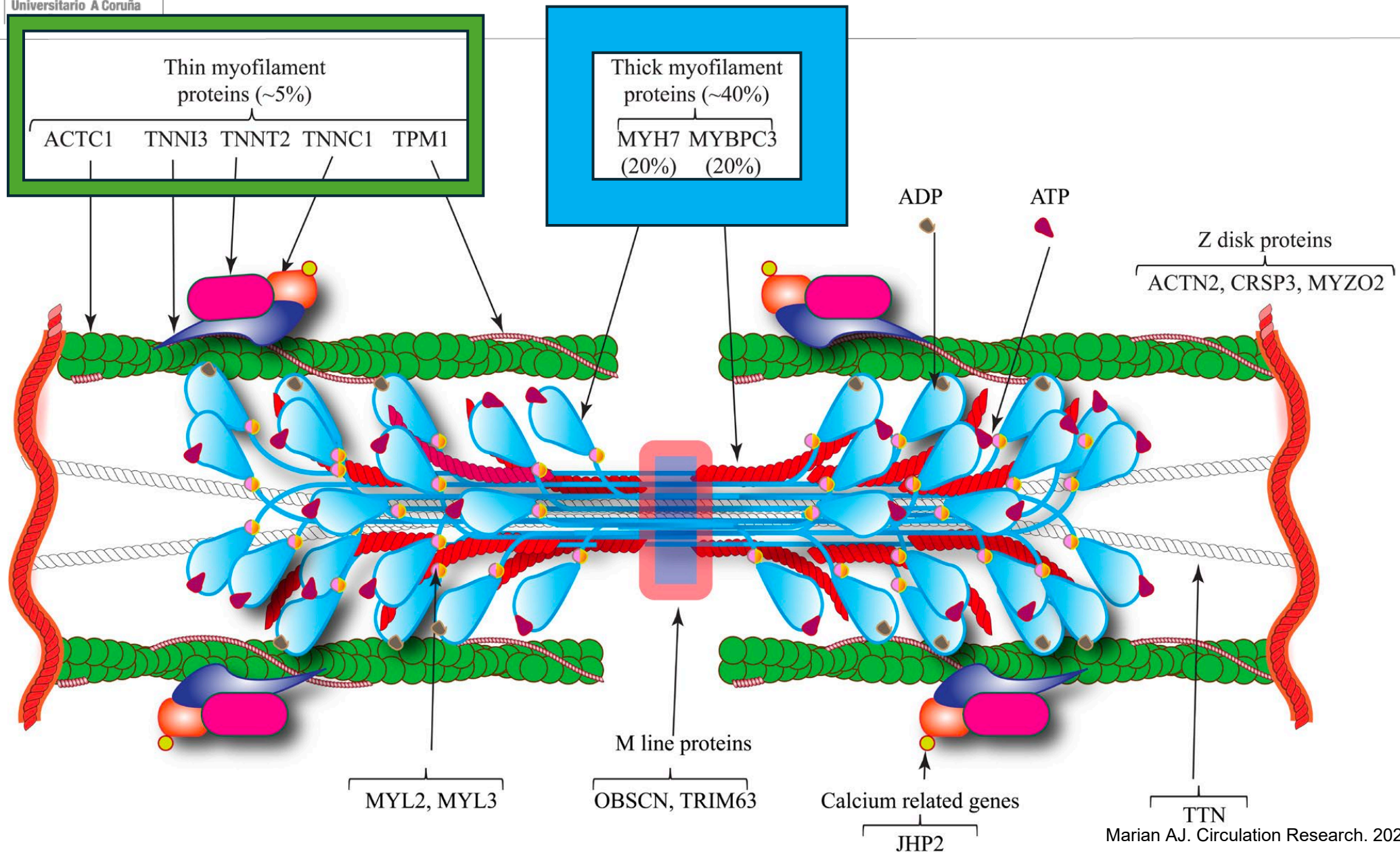
HCM myocardium is **HYPERCONTRACTILE**



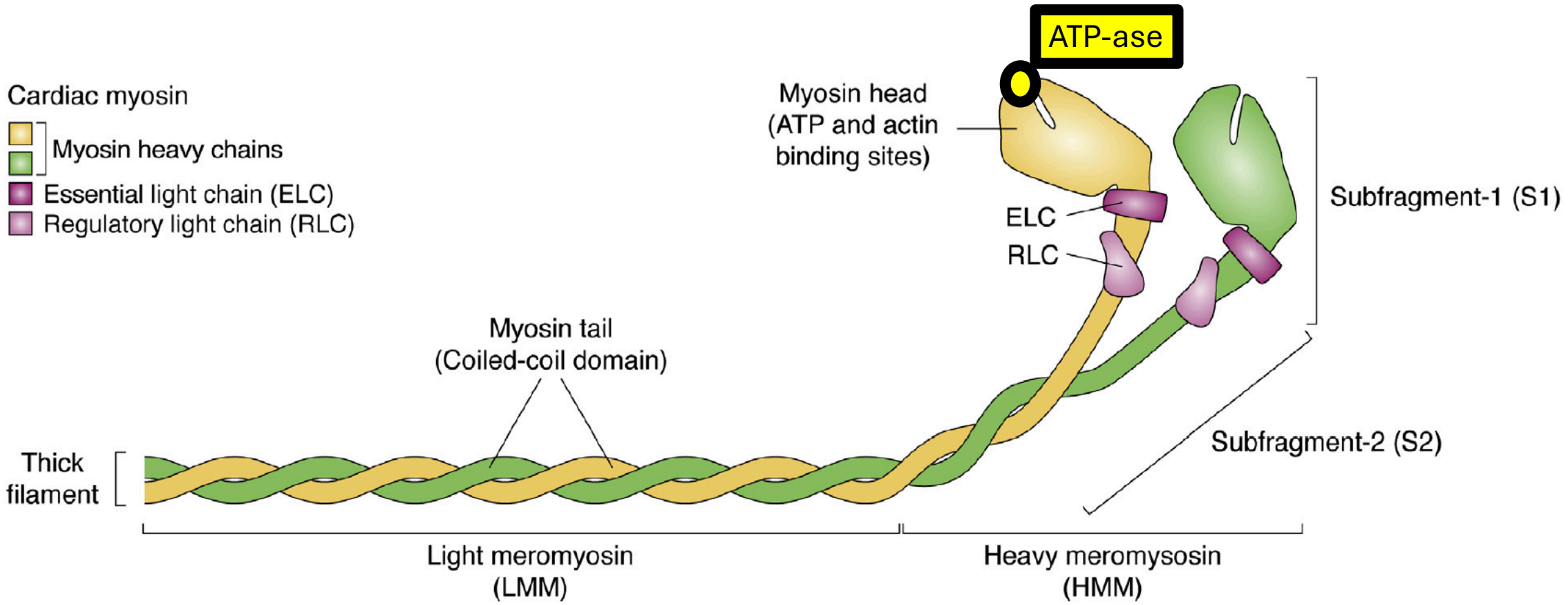


SARCOMERE



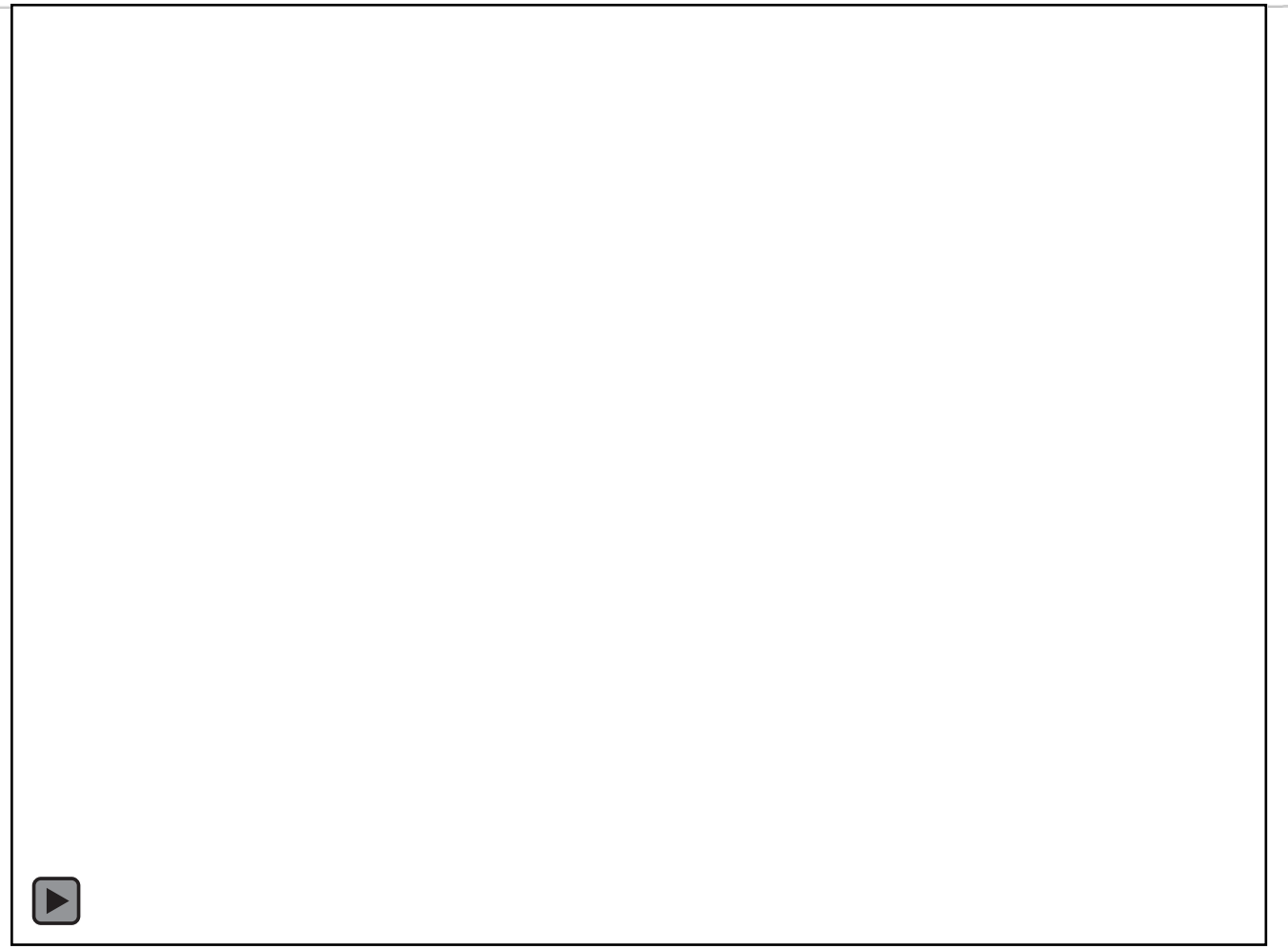
Marian AJ. Circulation Research. 2021;128:1533–1553

CARDIAC MYOSIN : “molecular” engine



Modified from Barrick SK, Greenberg MJ. J Biol Chem. 2021 Nov;297(5):101297

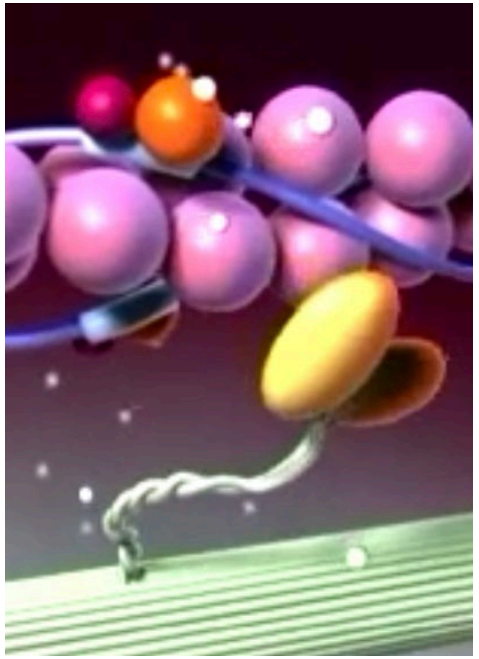
“Sliding Filament” theory or “Swinging cross-bridge” model

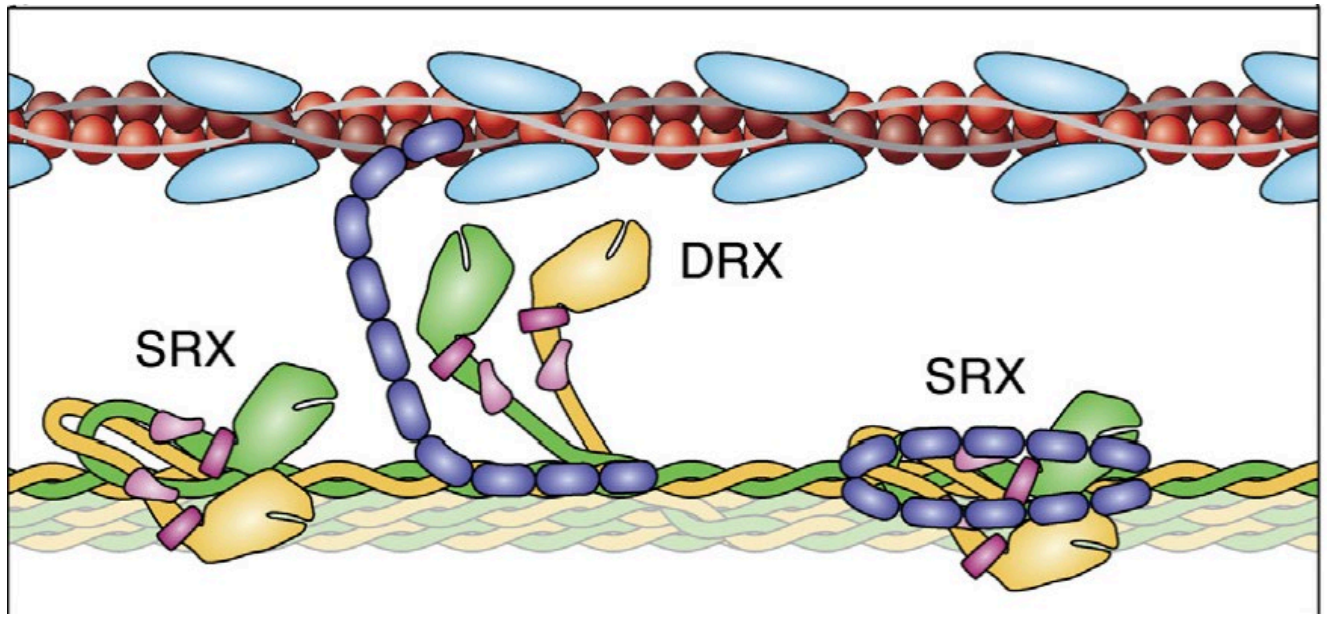


The **FORCE** generated by the muscle is proportional to the **NUMBER of actin-myosin cross bridges** that form

Video from YouTube; steps of muscle contraction; digital storytelling class

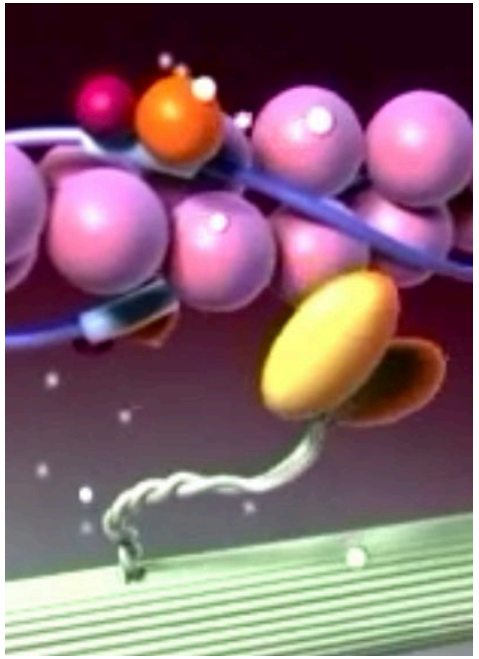
“Swinging lever arm” model

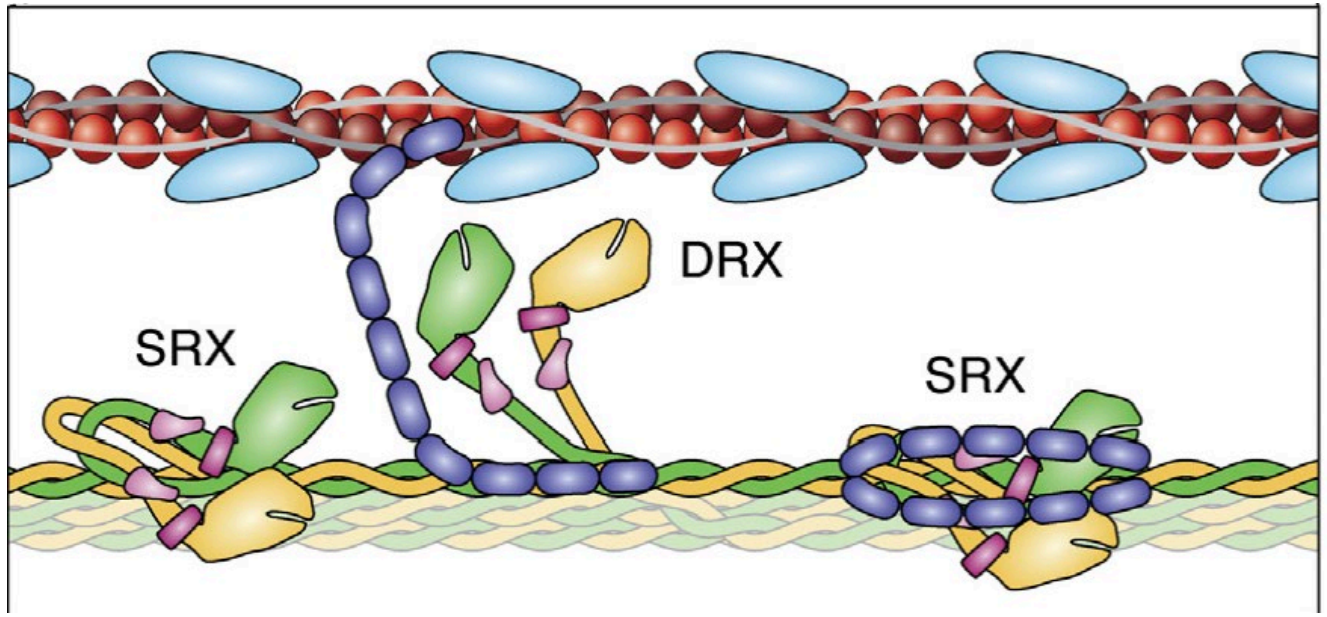




Barrick SK, Greenberg MJ. J Biol Chem. 2021 Nov;297(5):101297
C. Suay-Corredera and J. Alegre-Cebollada. FEBS Letters n/a, doi:https://doi.org/10.1002/1873-3468.14301 (2022).

3 ”DIFFERENT” MYOSIN CONFIGURATIONS





”Active”

Disordered-Relaxed
DRX

Super-relaxed
SRX

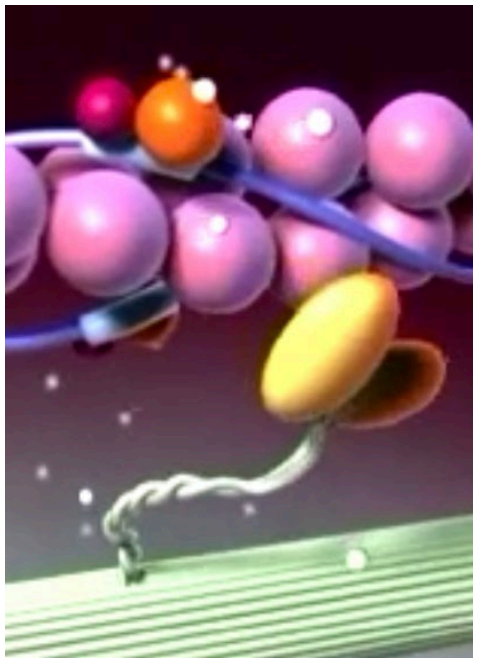
Maximum ATP hydrolysis rate

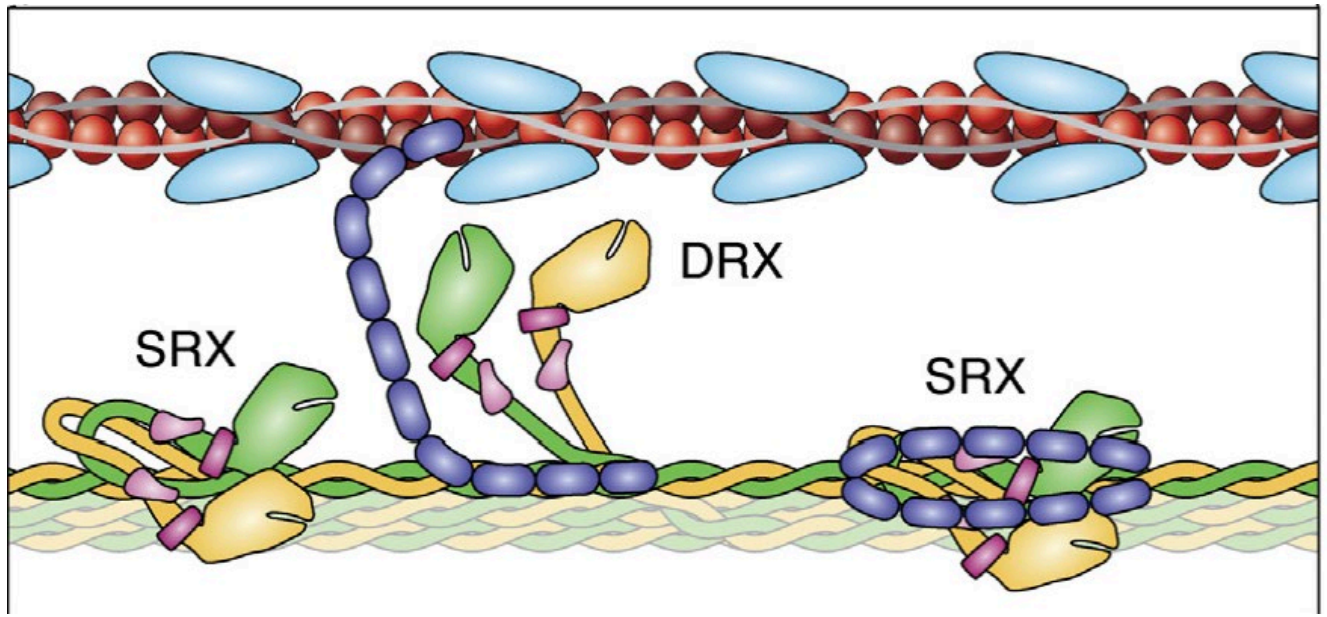
ATP

Minimum ATP hydrolysis rate

Barrick SK, Greenberg MJ. J Biol Chem. 2021 Nov;297(5):101297
C. Suay-Corredera and J. Alegre-Cebollada. FEBS Letters n/a, doi:https://doi.org/10.1002/1873-3468.14301 (2022).

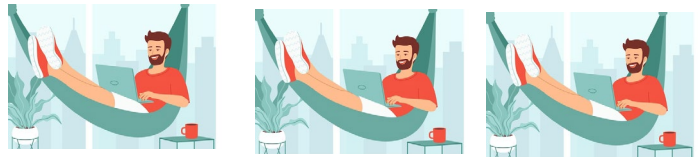
3 ”DIFFERENT” MYOSIN CONFIGURATIONS





Disordered-Relaxed
DRX

Super-relaxed
SRX

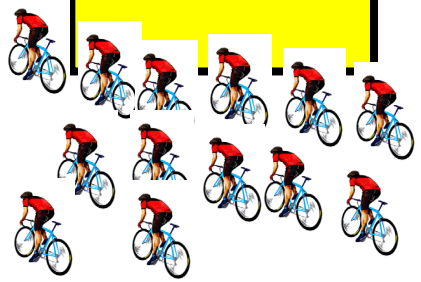


Barrick SK, Greenberg MJ. J Biol Chem. 2021 Nov;297(5):101297
C. Suay-Corredera and J. Alegre-Cebollada. FEBS Letters (2022).

3 ”DIFFERENT” MYOSIN CONFIGURATIONS

Exercise, temperature, *MYH7, MYBPC3* GENETIC VARIANTS, etc.

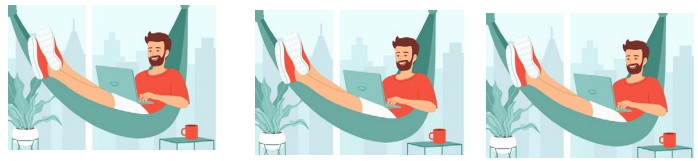
”Active”



Disordered-Relaxed
DRX

Super-relaxed
SRX

50%



Barrick SK, Greenberg MJ. J Biol Chem. 2021 Nov;297(5):101297
C. Suay-Corredera and J. Alegre-Cebollada. FEBS Letters (2022).

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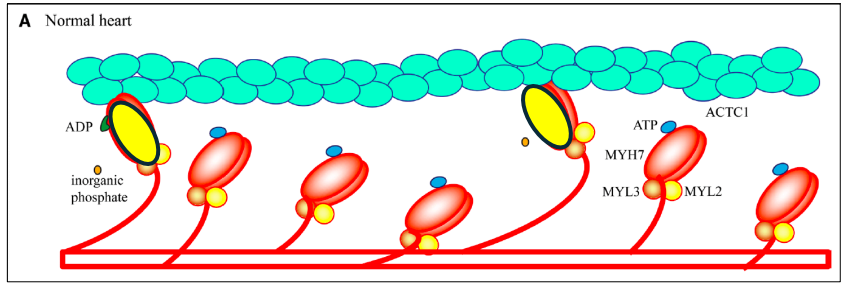
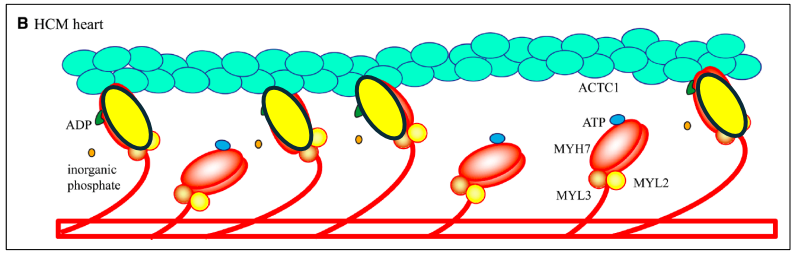
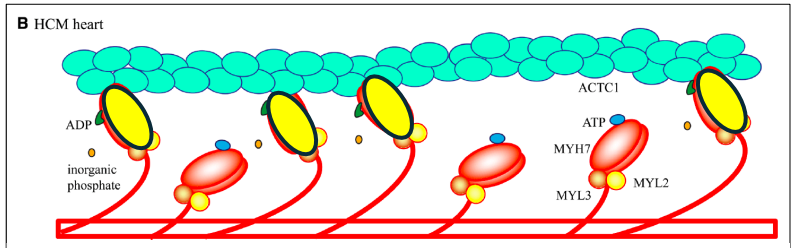
Sarcomeric pathogenic genetic variants etc,...

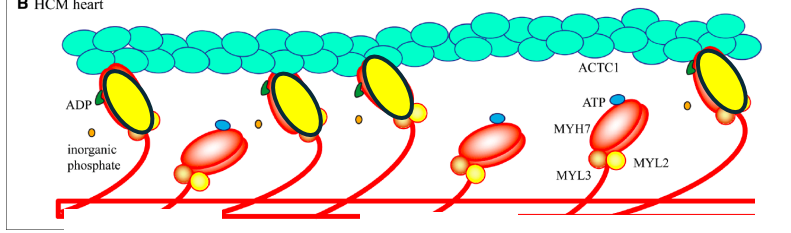
HCM

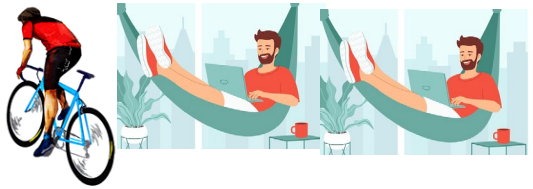
NORMAL HEART











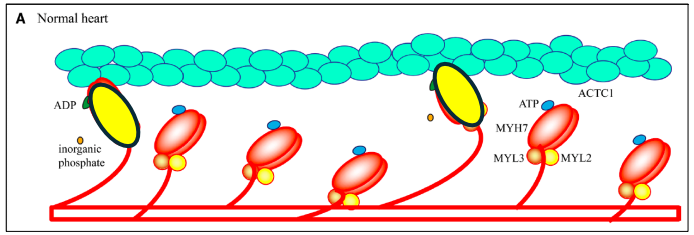
MYOSIN INHIBITORS

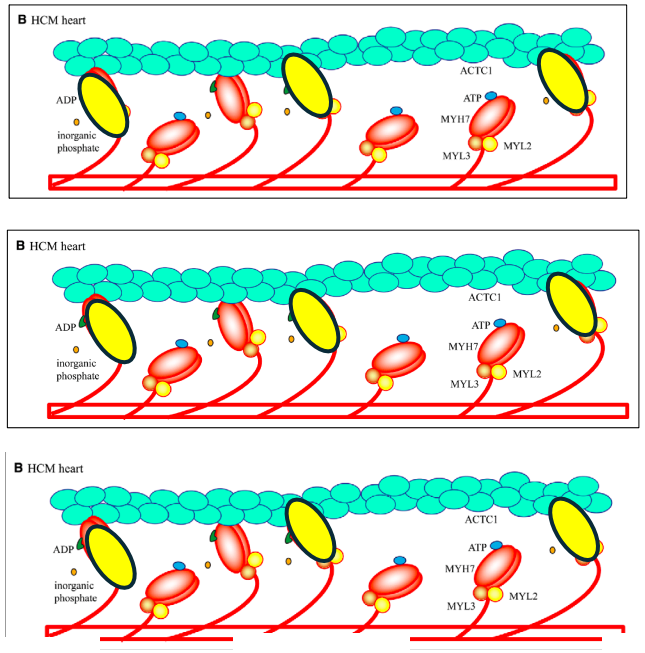
Disease Modyfing Treatment

Modificado de Marian AJ. Circulation Research. 2021;128:1533–1553

HCM

NORMAL HEART



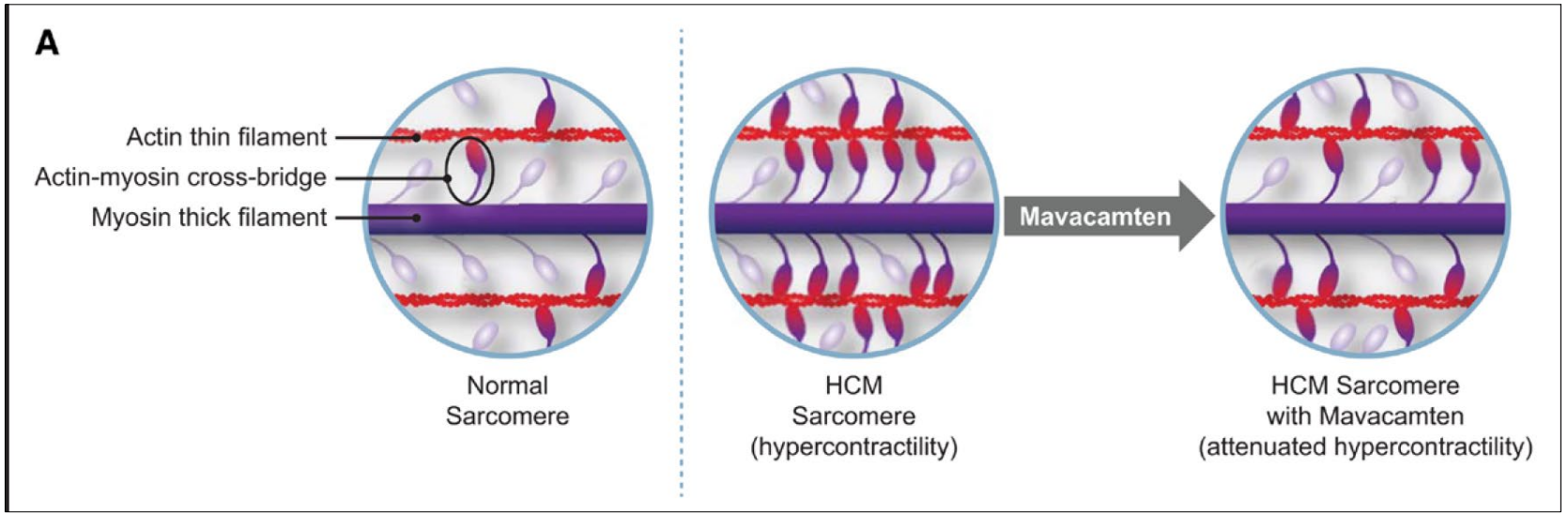


HCM Hypercontractility

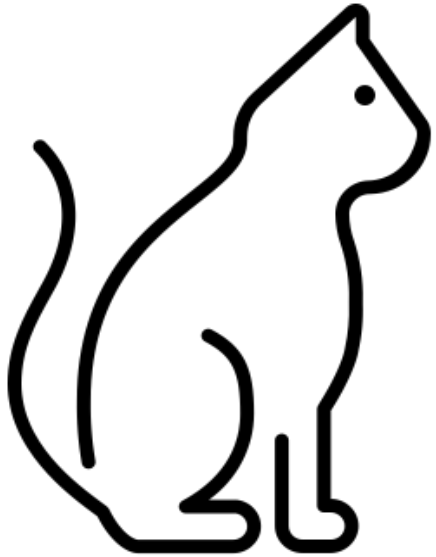
Modificado de Marian AJ. Circulation Research. 2021;128:1533–1553

MAVACAMTEN

First-in-class allosteric inhibitor of cardiac β myosin ATPase



↓ Actin-Myosin AFFINITY



↓

- HYPERCONTRACTILITY
- SAM
- LVOTO

Stern JA et al. PLoS One.2016
Green EM et al. Science 2016

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MAVACAMTEN in OBSTRUCTIVE HCM

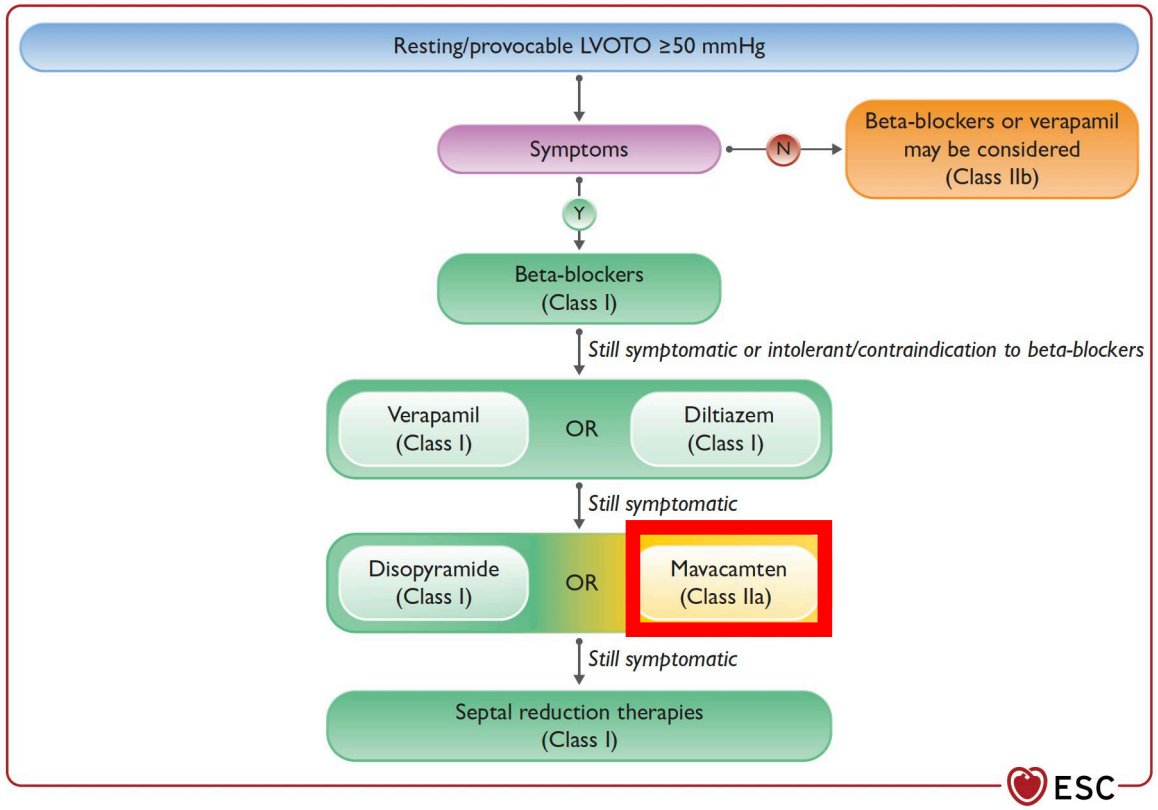
PHASE 3 CLINICAL TRIALS

EXPLORER-HCM
251 patients

ValorHCM
112 patients

EXPLORER-CN
MAVACAMTEN CHINA PHASE III
81 patients

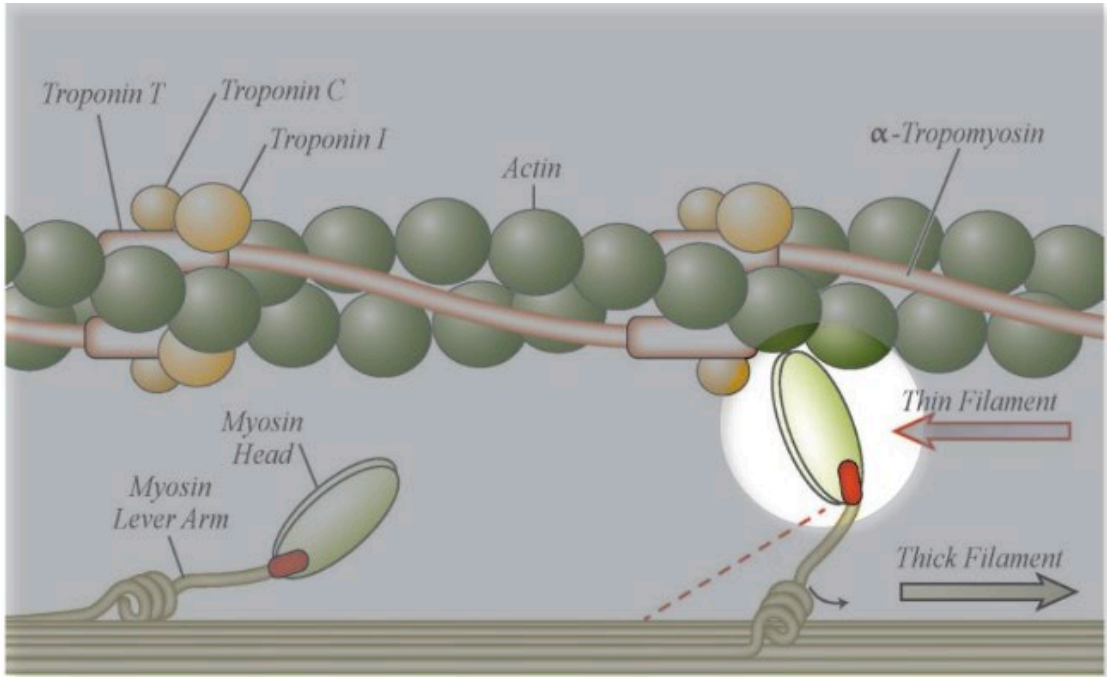
ESC 2023 GUIDELINES



Olivotto I et al. EXPLORER-HCM. Lancet 2020;396(10253):759–69
Desai MY et al. VALOR-HCM. J Am Coll Cardiol 2022;80(2):95–108
Tian C et al. EXPLORER-CN. JAMA Cardiol 2023;8(10):957
Arbelo E et al. 2023 ESC Cardiomyopathies Guidelines

AFICAMTEN

Next-in-class myosin inhibitor



PHASE 3 CLINICAL TRIALS (oHCM)

SEQUOIA HCM

282 patients

MAPLE HCM

"ON-GOING"

Maron MS et al. SEQUOIA-HCM. N Engl J Med 2024.

FUTURE

NON-OBSTRUCTIVE HCM

PHASE 3 CLINICAL TRIALS (Aficamten)

ACACIA HCM

ON-GOING

PHASE 3 CLINICAL TRIALS (Mavacamten)

ODYSSEY HCM

ON-GOING

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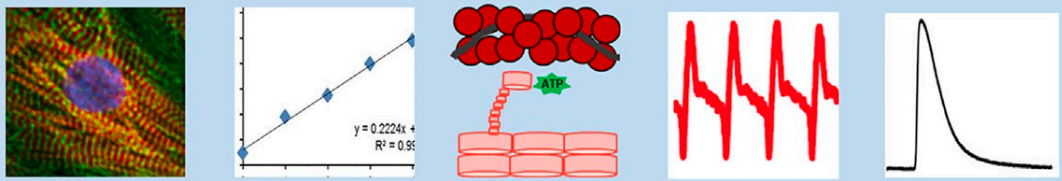
OTHER TARGETS: PEDIATRIC PATIENTS

Pediatric HCM patient and Crispr-edited iPSCs	**Monogenic, digenic and biallelic variant iPSCs (*MYH7*, *MYBPC3*, *TNNI3*) vs isogenic controls**
Cardiomyocytes & Biowires	
Assays	 Sarcomere organization; ATPase activity; Myosin-actin binding; Contractility, relaxation; Calcium transients
Drug response	**Complete rescue with myosin-targeted drugs compared to non-targeted drugs**
Clinical significance	**Highlights need for pediatric trials of myosin-targeted drugs**

Cell Reports Medicine

CellPress OPEN ACCESS

Article

Myosin inhibitor reverses hypertrophic cardiomyopathy in genotypically diverse pediatric iPSC-cardiomyocytes to mirror variant correction

Caroline Kinnear,[1] Abdelrahman Said,[1] Guoliang Meng,[2] Yimu Zhao,[3,4] Erika Y. Wang,[5] Naimeh Rafatian,[3] Neha Parmar,[1] Wei Wei,[2] Filio Billia,[4,6] Craig A. Simmons,[3,7,8] Milica Radisic,[3,4,9,10] James Ellis,[2,11,14,*] and Seema Mital[1,6,12,13,14,15,*]

PHASE 3 CLINICAL TRIALS (Aficamten)

CEDAR HCM

"ON-GOING"

PHASE 3 CLINICAL TRIALS (Mavacamten)

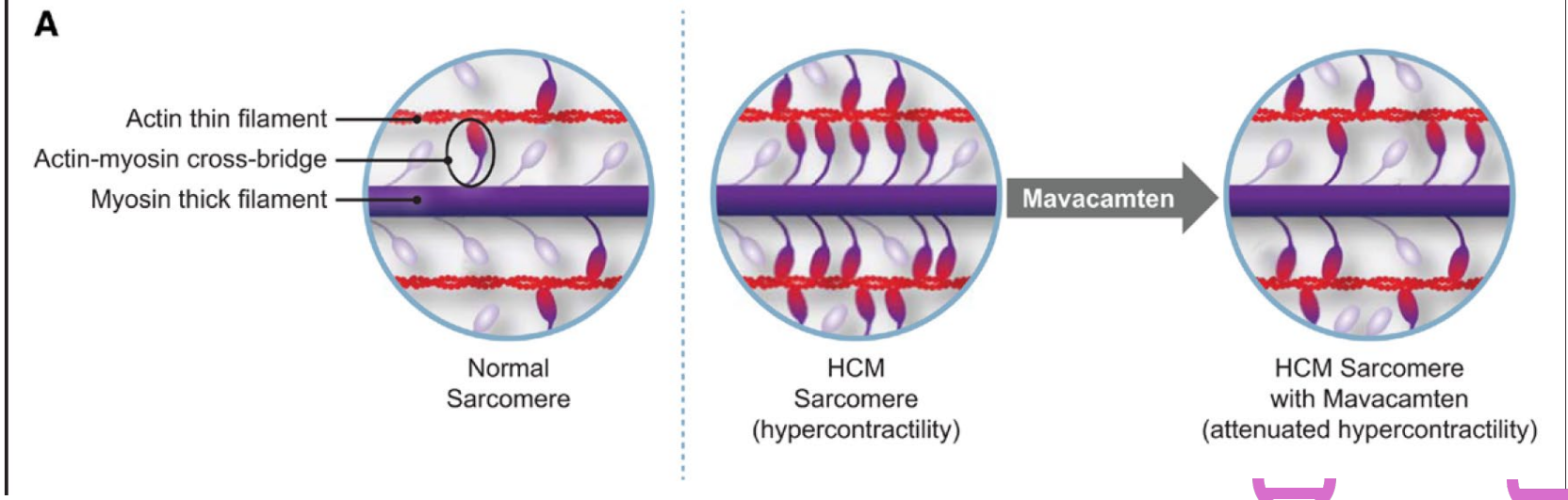
SCOUT HCM

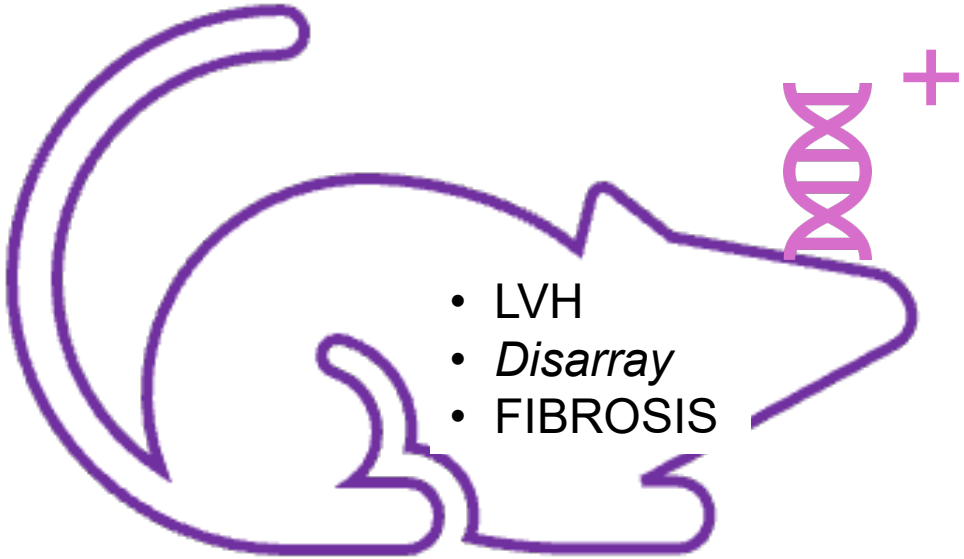
"ON-GOING"

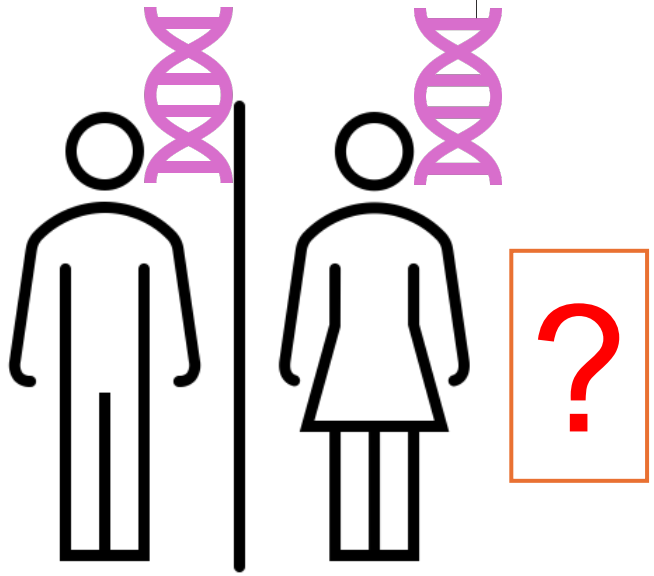
Kinnear et al., 2024, Cell Reports Medicine 5, 101520

MAVACAMTEN

First-in-class allosteric inhibitor of cardiac β myosin ATPase







Stern JA et al. PLoS One.2016
Green EM et al. Science 2016

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OTHER TARGETS: SARCOMERE MODULATOR

365
JACC April 2, 2024
Volume 83, Issue 13, Suppl A

Heart Failure and Cardiomyopathies

CHRONIC TREATMENT WITH THE NOVEL SARCOMERE MODULATOR EDG-7500 IMPROVES LEFT VENTRICULAR DISTENSIBILITY AND CARDIAC OUTPUT RECRUITMENT UNDER STRESS IN A MINI-PIG GENETIC MODEL OF NON-OBSTRUCTED HYPERTROPHIC CARDIOMYOPATHY

Moderated Poster Contributions
Moderated Poster Theater 03
Sunday, April 7, 2024, 3:15 p.m.-3:25 p.m.

Session Title: From the Bench to the Bedside: Advances in He
Abstract Category: 06. Heart Failure and Cardiomyopathies: E
Presentation Number: 1087-05

Authors: Marc Evanchik, Craig Emter, Carlos L. del Rio, Emily Peter, Alan Russell, Marc J. Semigran, Edgewise Therapeutic

Background: Exercise intolerance due to decreased cardiac output recruitment under stress and increased left ventricular (LV) filling pressures with diastolic dysfunction are hallmarks of hypertrophic cardiomyopathy (HCM). EDG-7500 is a novel first-in-class oral, selective, cardiac sarcomere modulator currently under evaluation in a Ph1 study. This *in vivo* study evaluated the chronic effects of EDG-7500 in a genetic pig model of non-obstructed HCM (nHCM) to test the hypothesis that EDG-7500 can alter disease progression and improve cardiac output recruitment under stress, a key determinant of exercise capacity.

A Study of EDG-7500 in Adult Patients With Obstructive Hypertrophic Cardiomyopathy (CIRRUS-HCM)

ClinicalTrials.gov ID NCT06347159

Sponsor Edgewise Therapeutics, Inc.

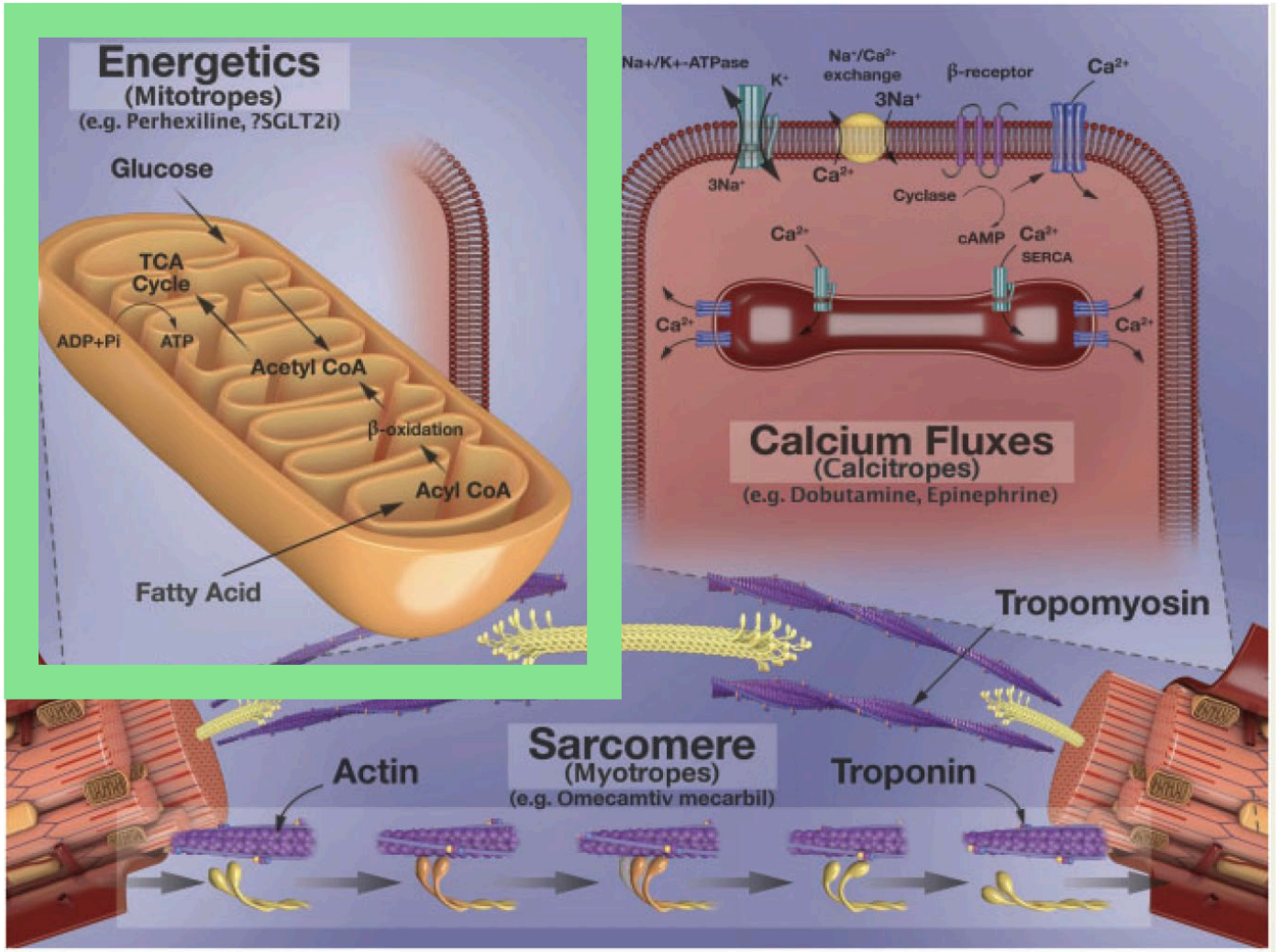
Information provided by Edgewise Therapeutics, Inc. (Responsible Party)

Last Update Posted 2024-05-08

PHASE 2: ON-GOING

https://clinicaltrials.gov/study/NCT06347159

OTHER TARGETS: IMPROVE MYOCARDIAL ENERGETICS

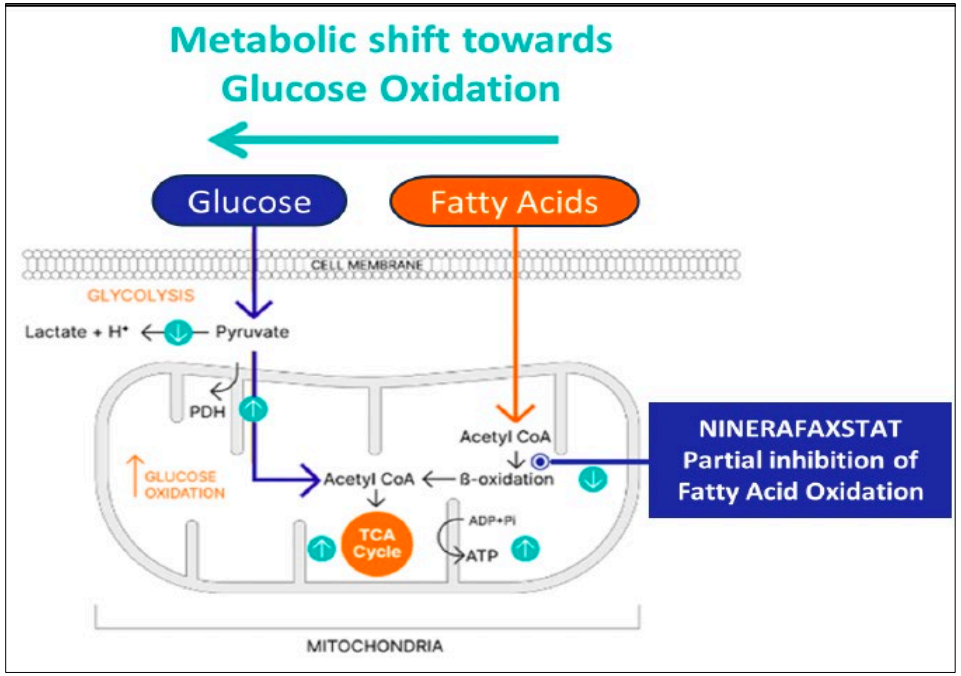


Desjardin JT et al. EHJ Acute Cardiovascular Care (2021) 10, 676–686

OTHER TARGETS: Improve myocardial energetics

ORIGINAL RESEARCH

Safety and Efficacy of Metabolic Modulation With Ninerafaxstat in Patients With Nonobstructive Hypertrophic Cardiomyopathy



PHASE 3: FORTITUDE-HCM

ON-GOING

A Study to Evaluate the Efficacy and Safety of Sotagliflozin in Symptomatic Obstructive and Non-obstructive Hypertrophic Cardiomyopathy (SONATA-HCM)

ClinicalTrials.gov ID NCT06481891

Sponsor Lexicon Pharmaceuticals

Information provided by Lexicon Pharmaceuticals (Responsible Party)

PHASE 3: SONATA-HCM

ON-GOING

Maron MS et al. J Am Coll Cardiol 2024 May 28;83(21):2037-2048.
https://clinicaltrials.gov/study/NCT06481891

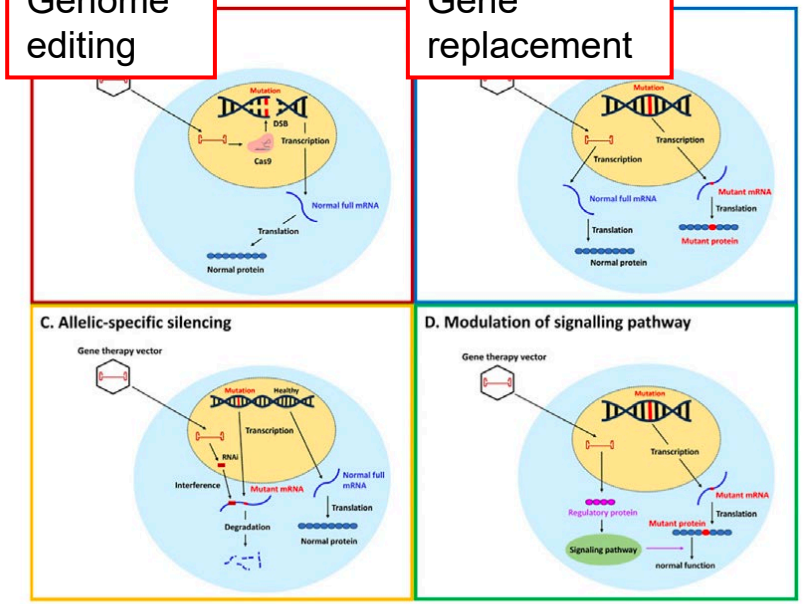
Servizo de Cardioloxía

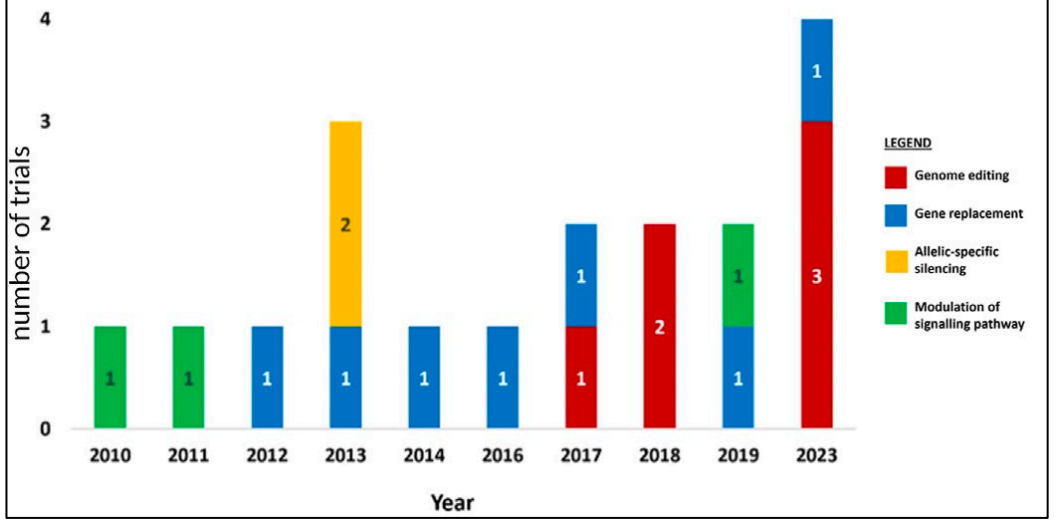
SERVIZO GALEGO de SAÚDE | Complexo Hospitalario Universitario A Coruña

OTHER TARGETS: GENE THERAPY

Genome editing

Gene replacement





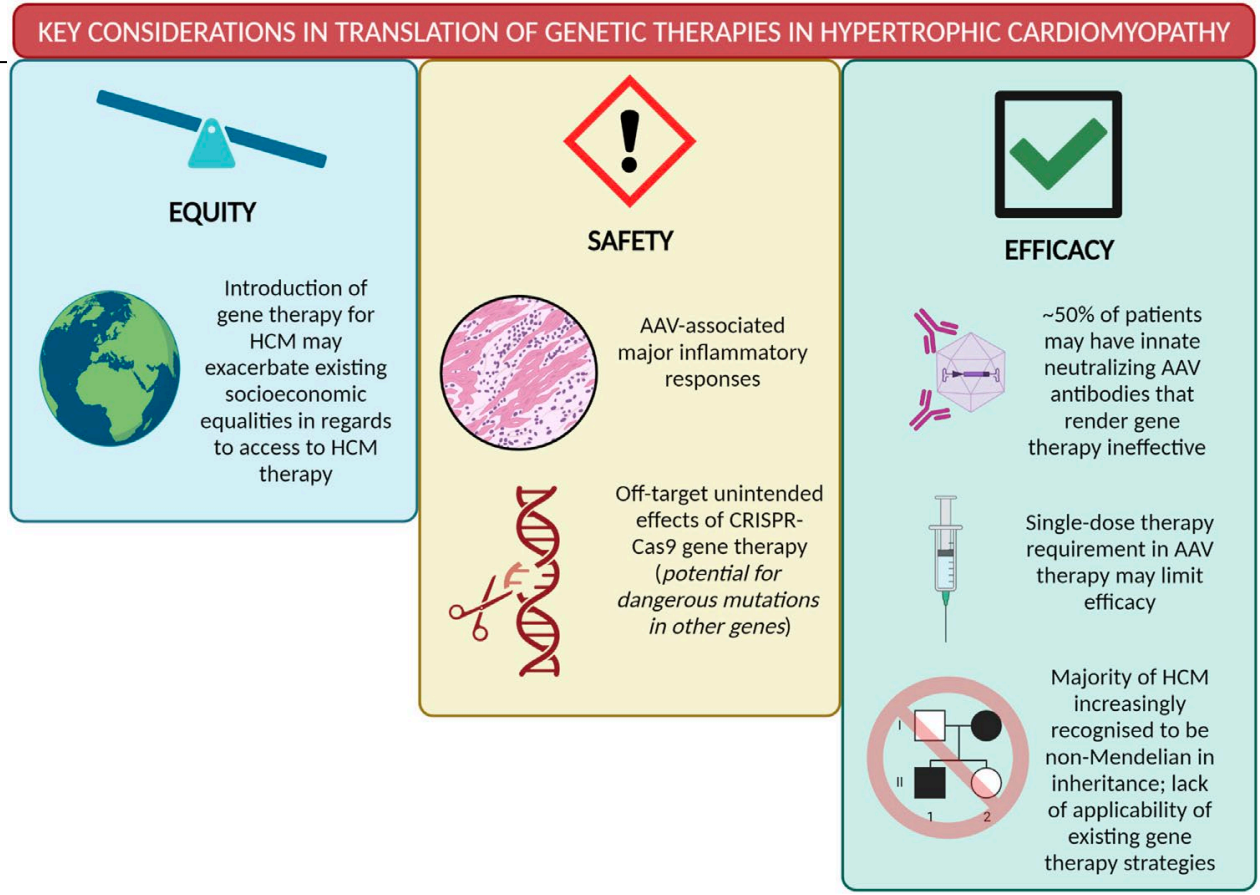
PHASE 1: ON-GOING

RECRUITING

Study of Safety and Tolerability of TN-201 in Adults With Symptomatic MYBPC3 Mutation-associated HCM (MyPEAK-1)

ClinicalTrials.gov ID NCT05836259

Sponsor Tenaya Therapeutics



Paratz ED et al. Canadian Journal of Cardiology 40 (2024) 777e788
https://clinicaltrials.gov/study/NCT05836259

The future of HCM is bright and promising...

Jorge Peteiro 2007
Coruña (fragment)
Private collection