The Avenue to Personalized Care for Cardiomyopathy Patients

William J. McKenna, MD DSc

CEO & Medical Director, Heart Hospital, HMC

Institutional Officer for Research, HMC

Associate Dean for Research, WCM-Q

Weill Cornell Medicine-Qatar


Arctic Ocean
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ARCTIC CIRCLE
66°30'N
ASIA
EUROPE
Caspian Sea
Black Sea
Aral Sea
Med. Sea
MIDDLE EAST
Qatar
TROPIC OF CANCER
23°5'N
Red Sea
Arabian Sea
Bay of Bengal
Pacific Ocean
AFRICA
Gulf of Aden
0°
EQUATOR
OCEANIA
Indian Ocean
TROPIC OF CAPRICORN
23°5'S
AUSTRALIA
1500 mi
1500 km
worldatlas


worldatlas
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Bahrain
Manama
Ar Ruways
Persian Gulf
Ar Khuwayr
Gulf of Bahrain
Qatar
Hawar Islands (Bahrain)
Al Khawr
25 mi
25 km
Umm Salal Ali
Dukhan
Doha
Ar Rayyan
Dawhat Salwa Bay
Umm Bab
Al Wakrah
Saudi Arabia
Umm Sa'id
Qurayn Abu al Bawl
Persian Gulf
Al Salwa
QATAR
LOW / HILLS / MOUNTAINS
U.A.E.
CLICK HERE FOR LARGER MAP

Women's Wellness & Research Center

Ambulatory Care Center

Qatar Rehabilitation Institute

Translational Research Institute

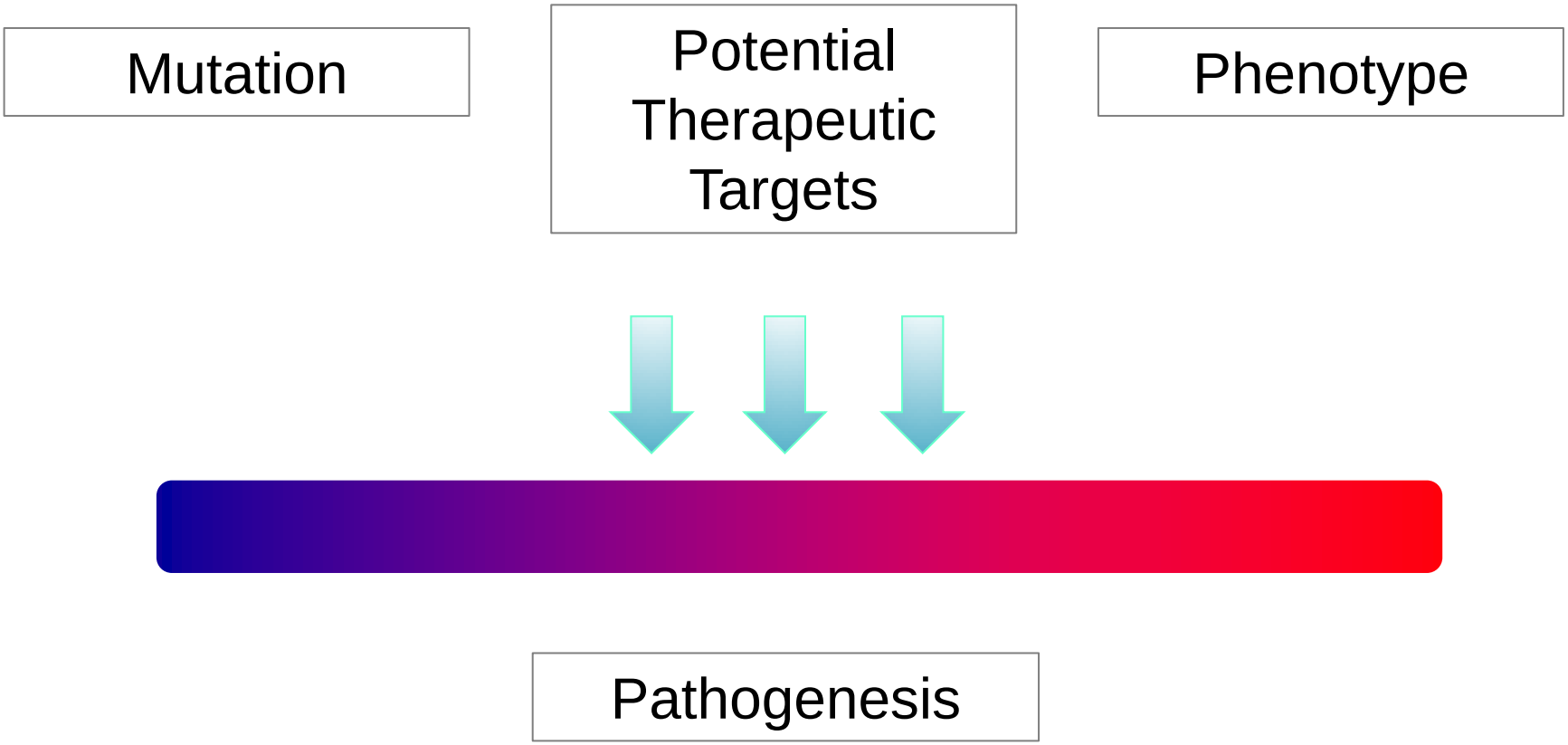
Personalized Medicine

Definition

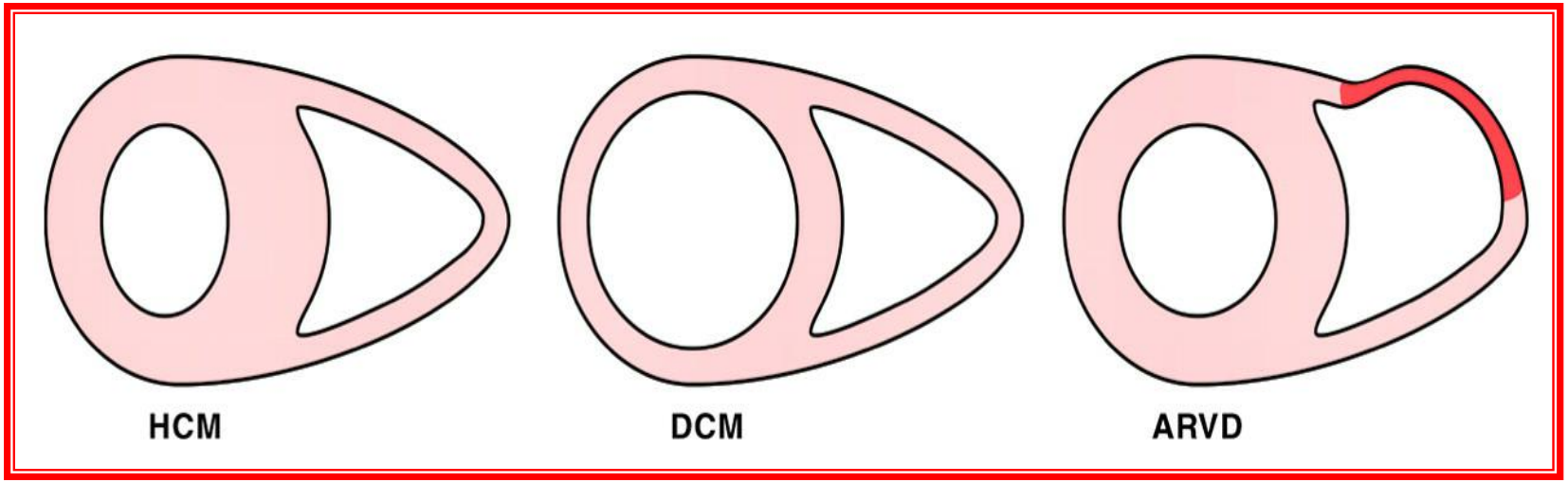
Customization of medical care tailored to the individual

- Biological
- Phenotypic
- Pyscho-social

Targeted/individualised treatment



The Genetic Basis of the Inherited Cardiomyopathies

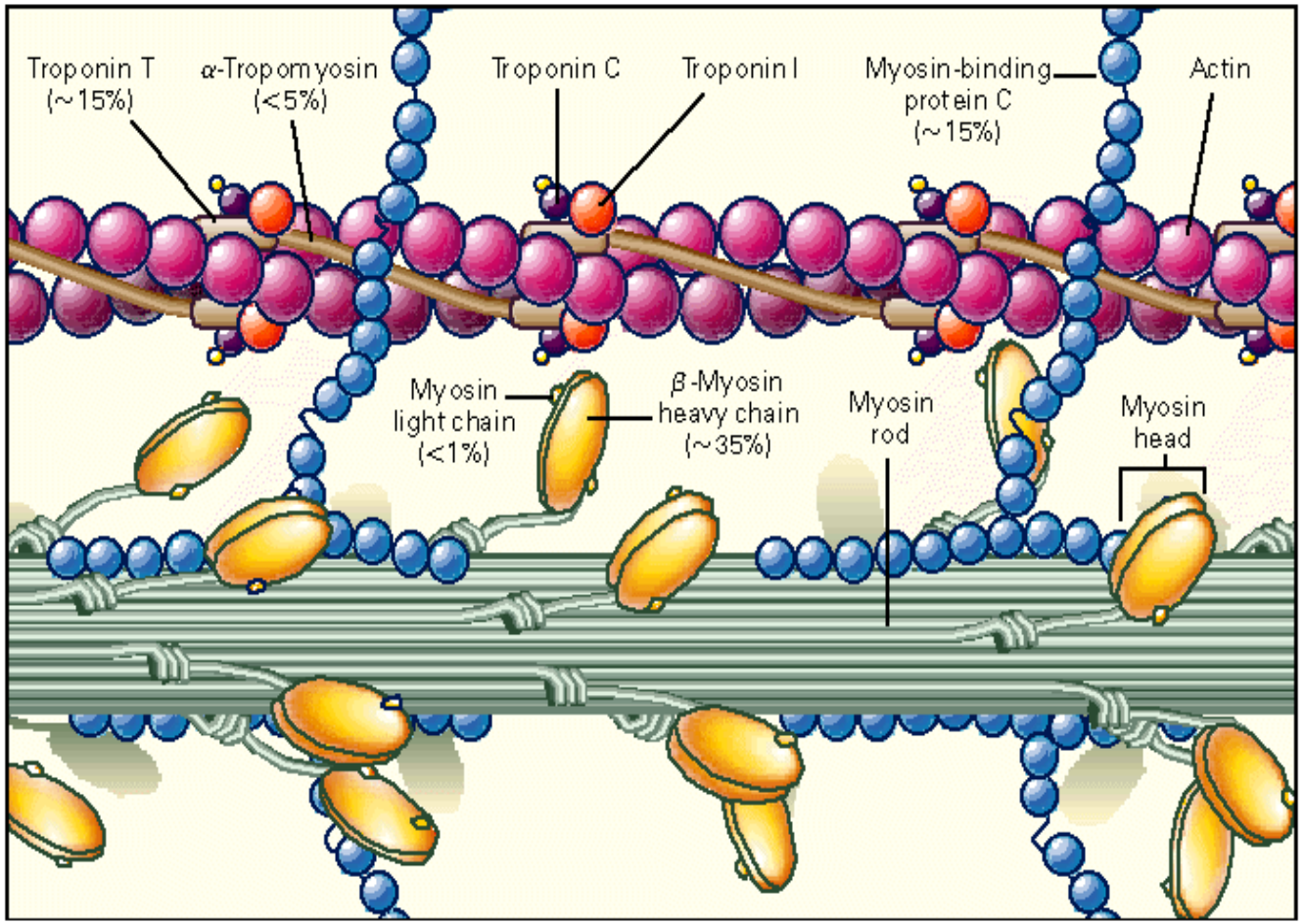


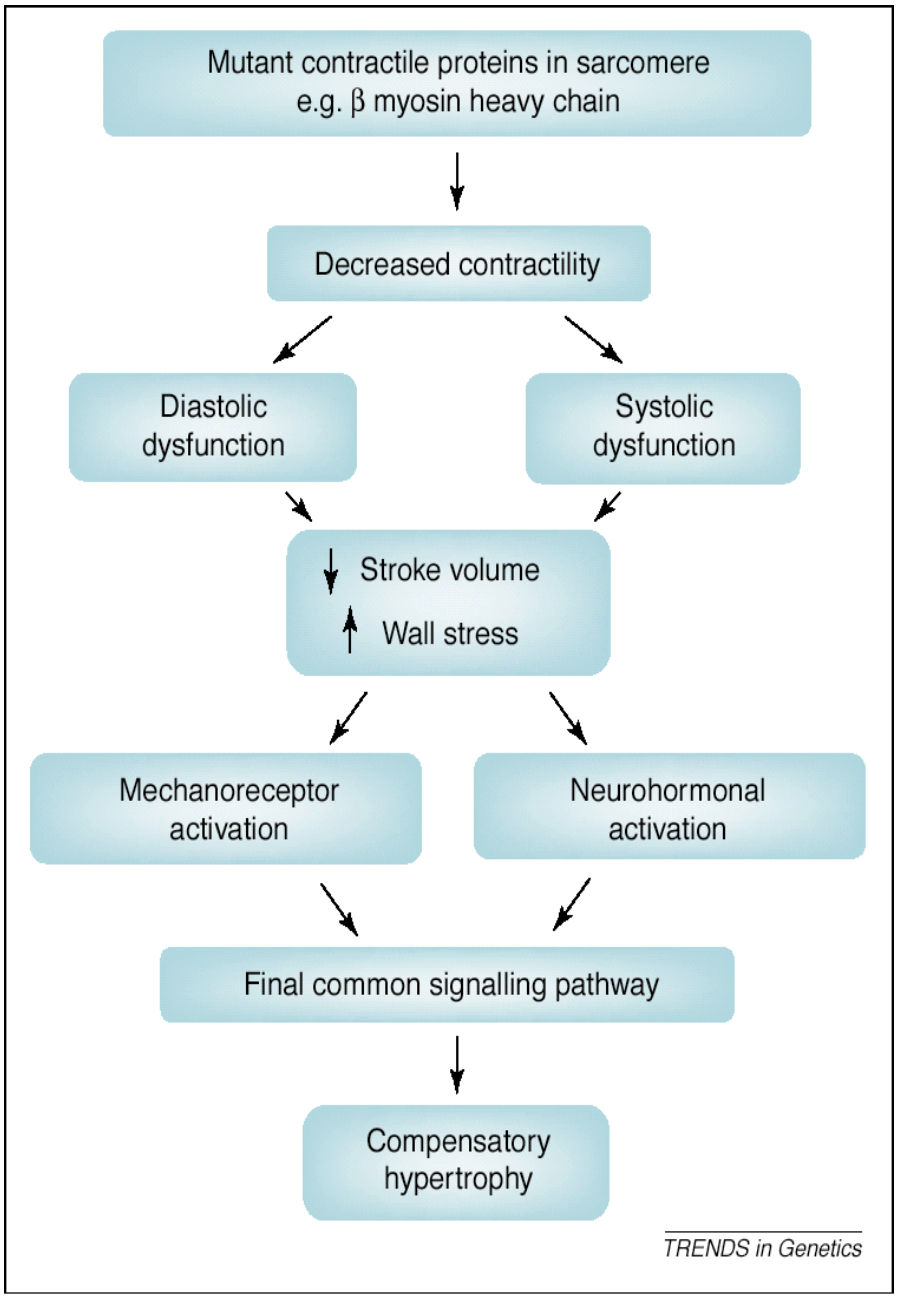
sarcomere

cytoskeletal
sarcomere
nuclear envelope

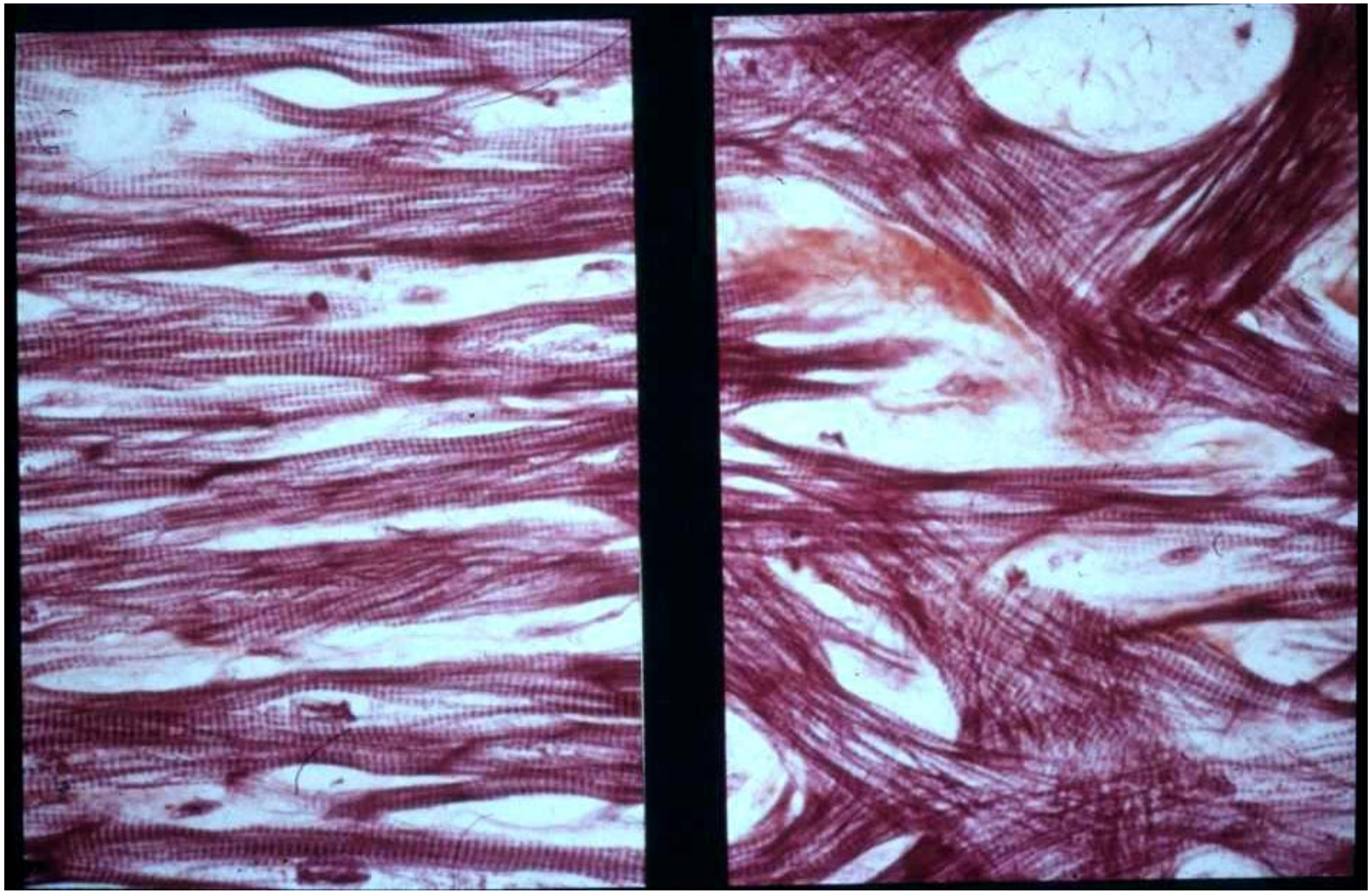
cell
adhesion

Sarcomere Disease



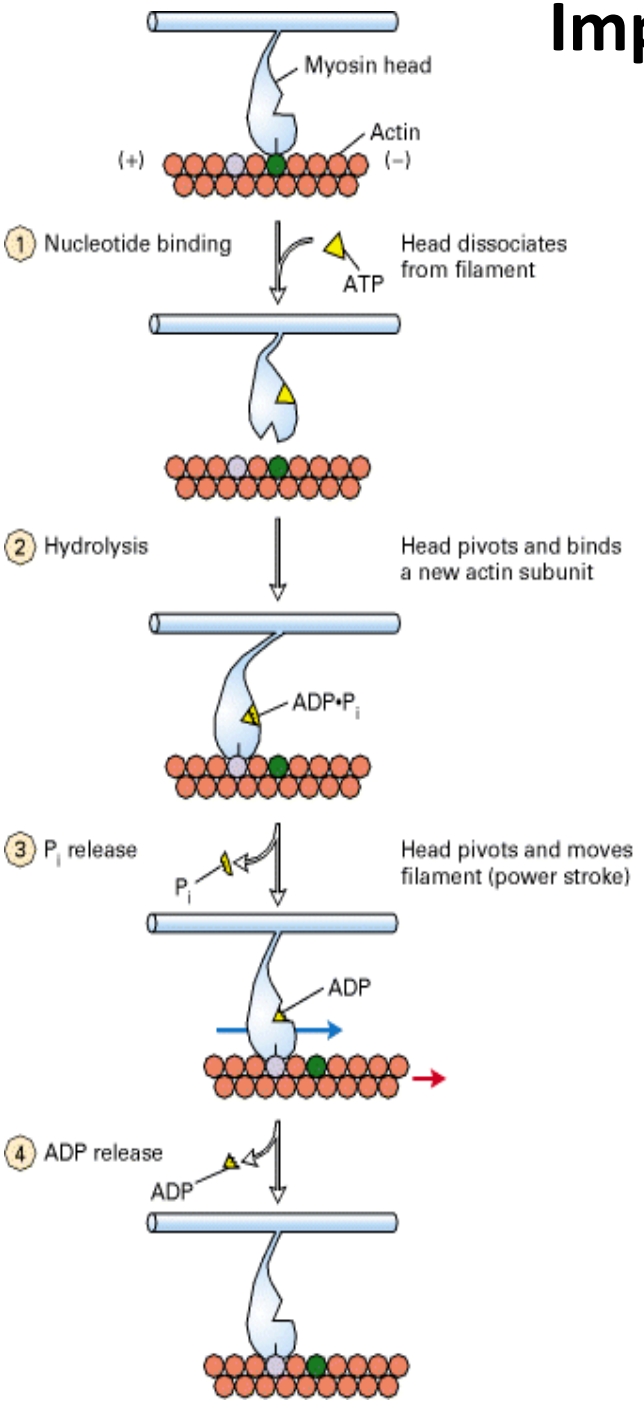

Mutant contractile proteins in sarcomere
e.g. β myosin heavy chain
Decreased contractility
Diastolic dysfunction
Systolic dysfunction
Stroke volume
Wall stress
Mechanoreceptor activation
Neurohormonal activation
Final common signalling pathway
Compensatory hypertrophy
TRENDS in Genetics

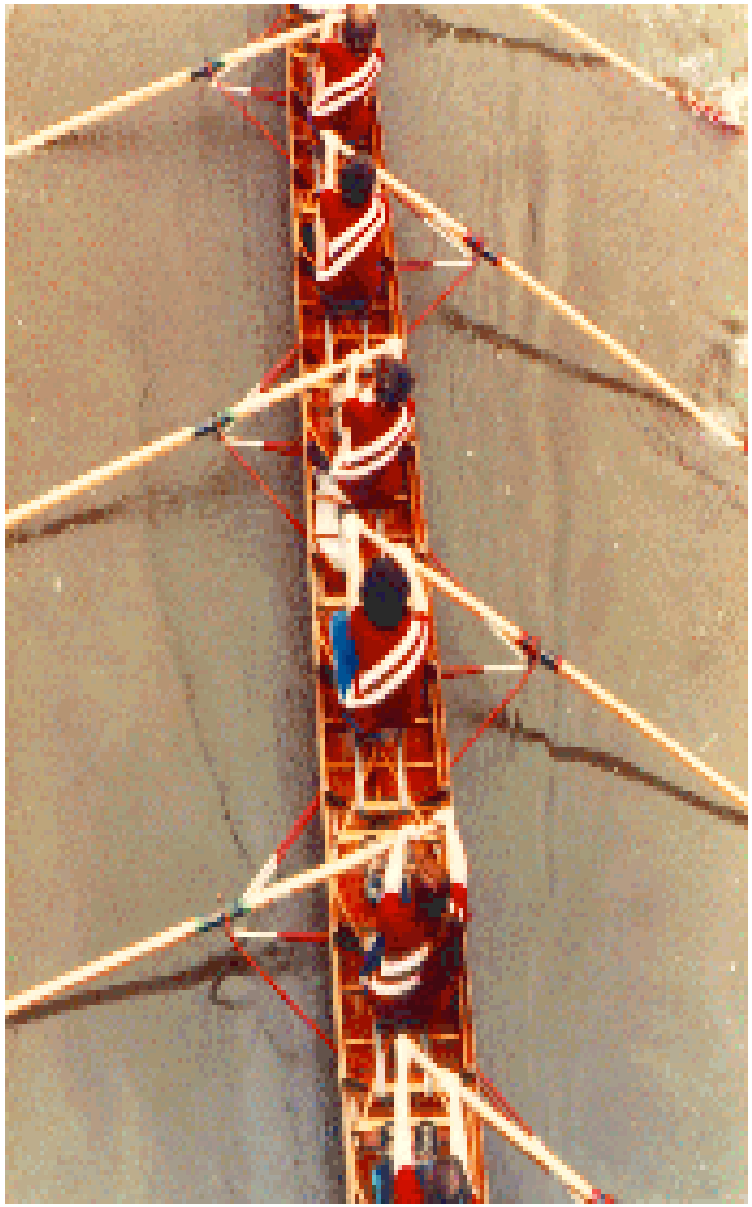
Hypertrophic Cardiomyopathy



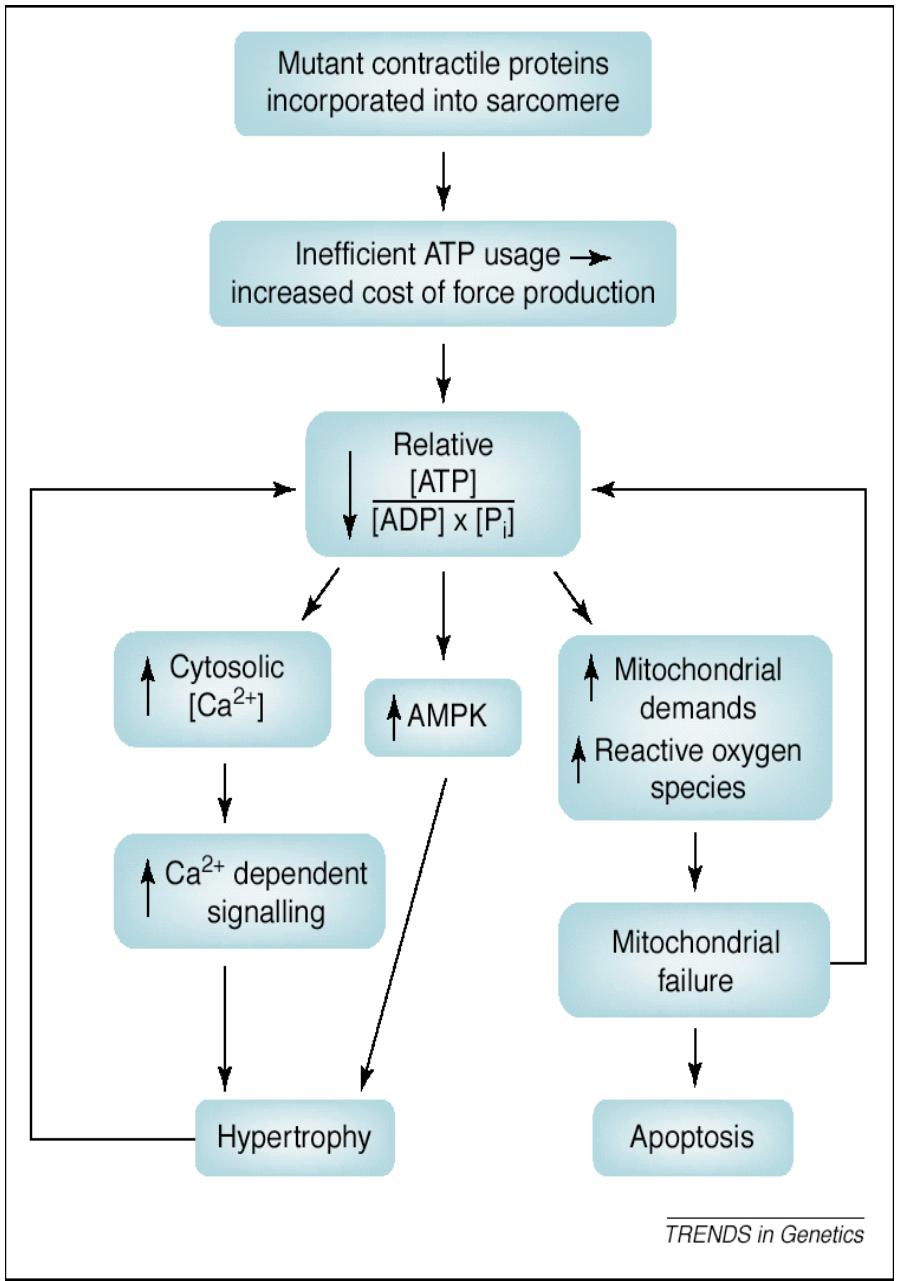
Rx – symptoms, prevent complications

Impaired efficiency of Force Generation



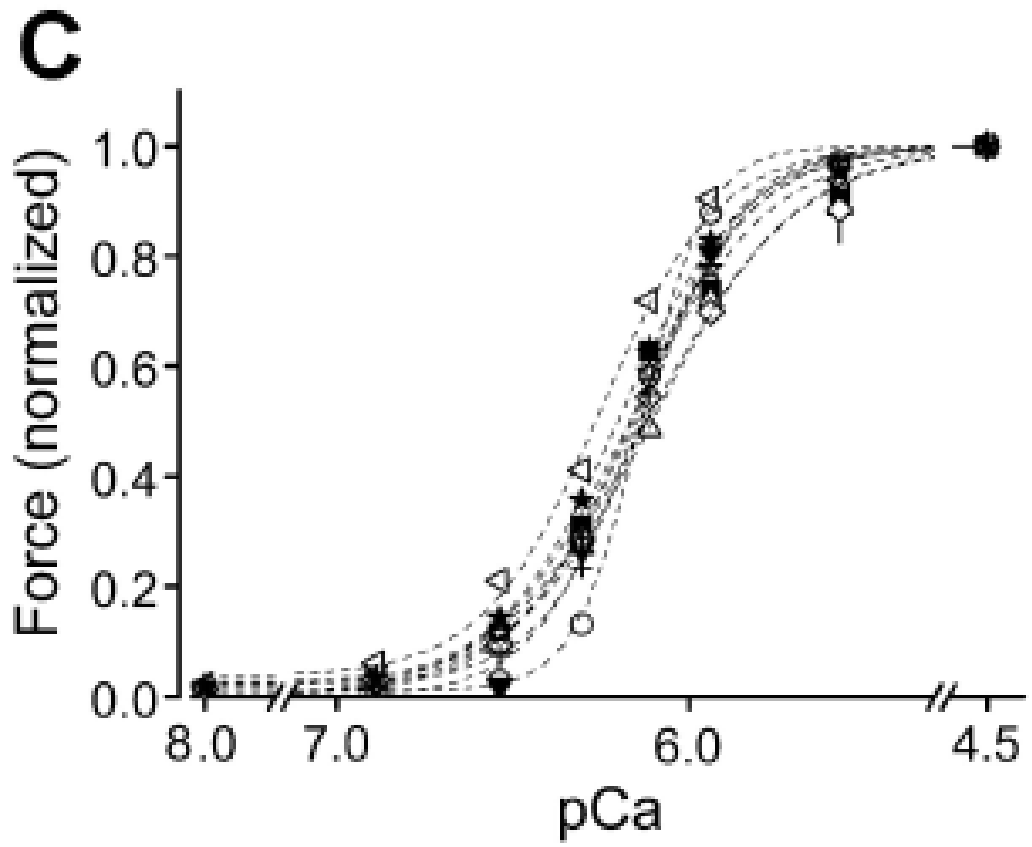


Energy Depletion Hypothesis



Controls (3) – single soleus muscle fibres (19)

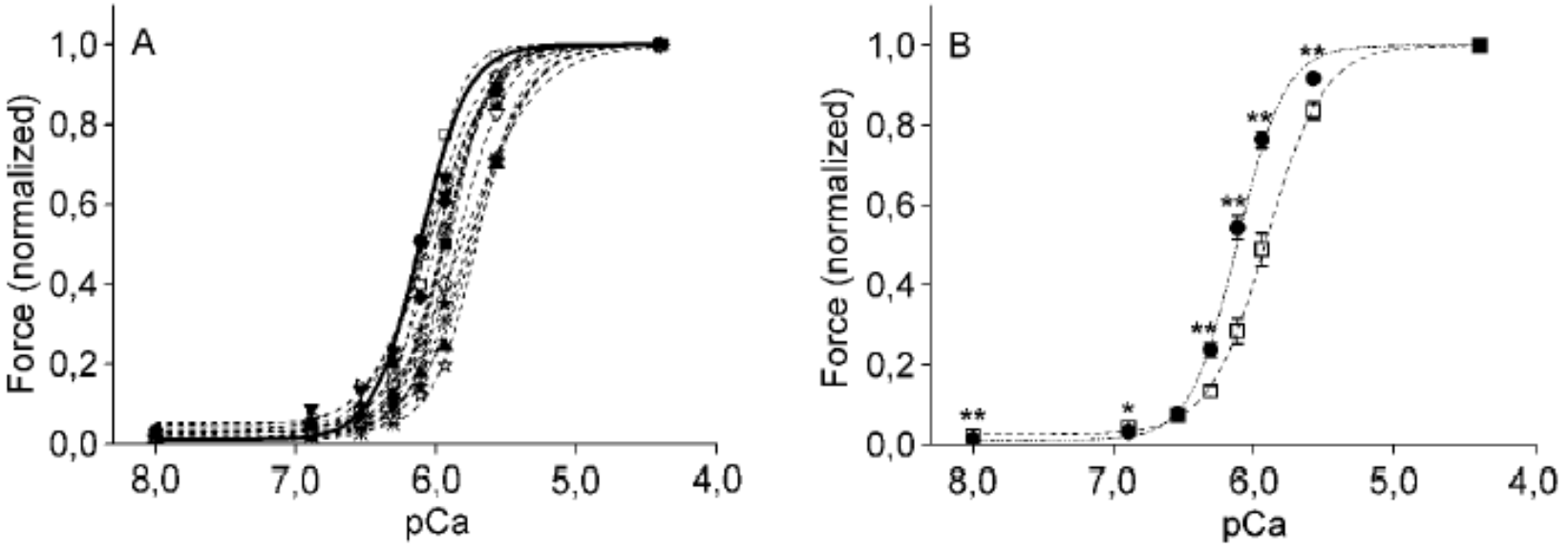
Relation of force / Ca sensitivity



Kirschner, *Am J Physiol Heart Circ Physiol* 288: H1242–H1251, 2005.

Beta myosin heavy chain disease – single soleus muscle fibres (16)

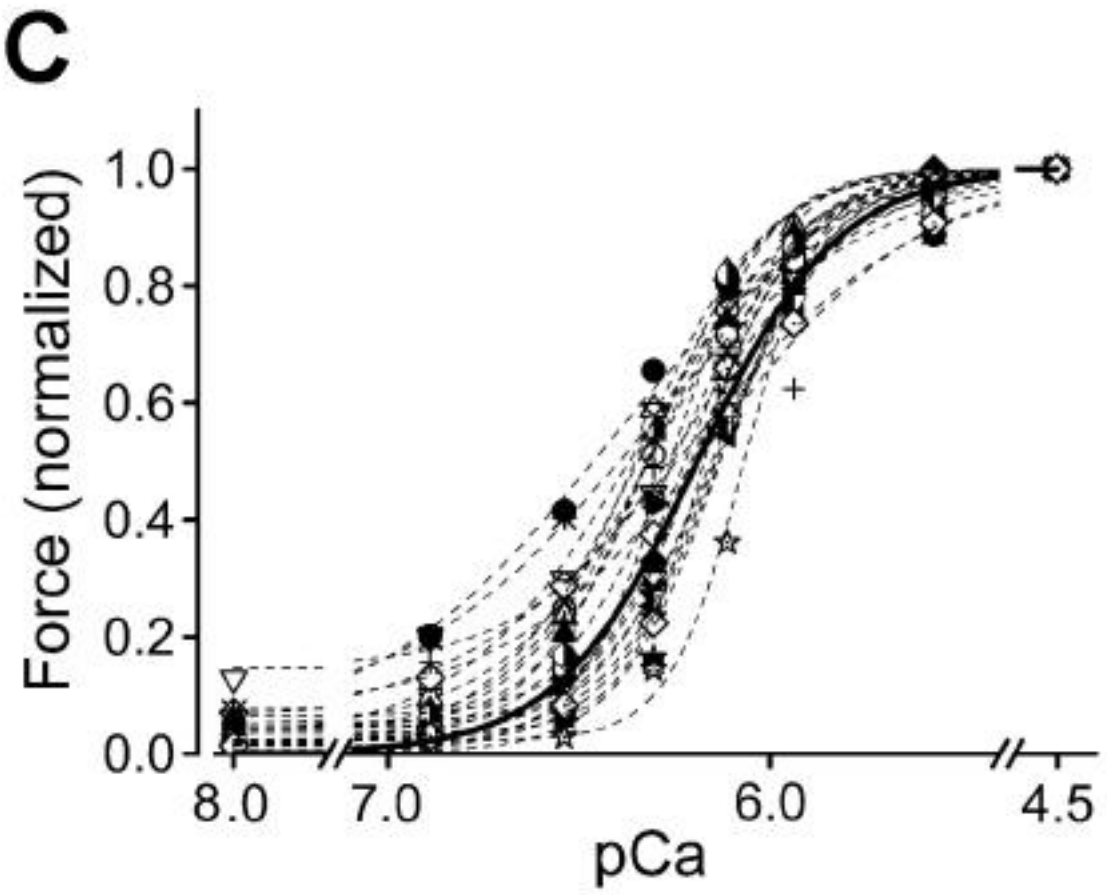
Relation of force / Ca sensitivity (Arg719Trp)



Kirschner, *Am J Physiol Heart Circ Physiol* 288: H1242–H1251, 2005.

Beta myosin heavy chain disease – single soleus muscle fibres (25)

Relation of force / Ca sensitivity (Ile736Thr)



Kirschner, *Am J Physiol Heart Circ Physiol* 288: H1242–H1251, 2005.

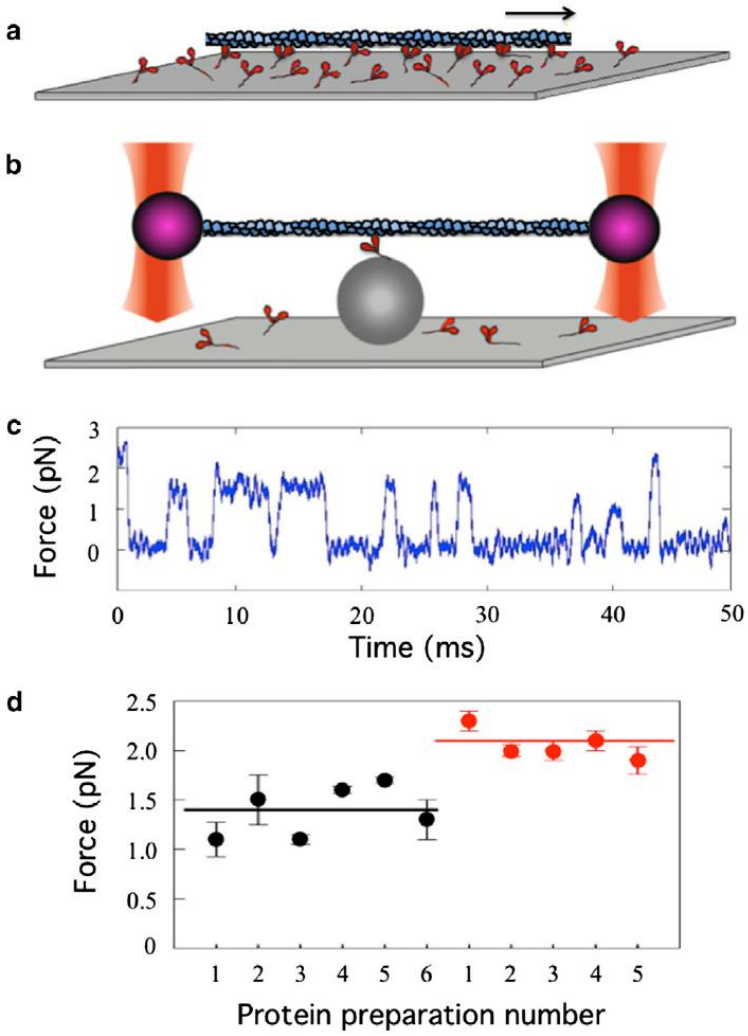
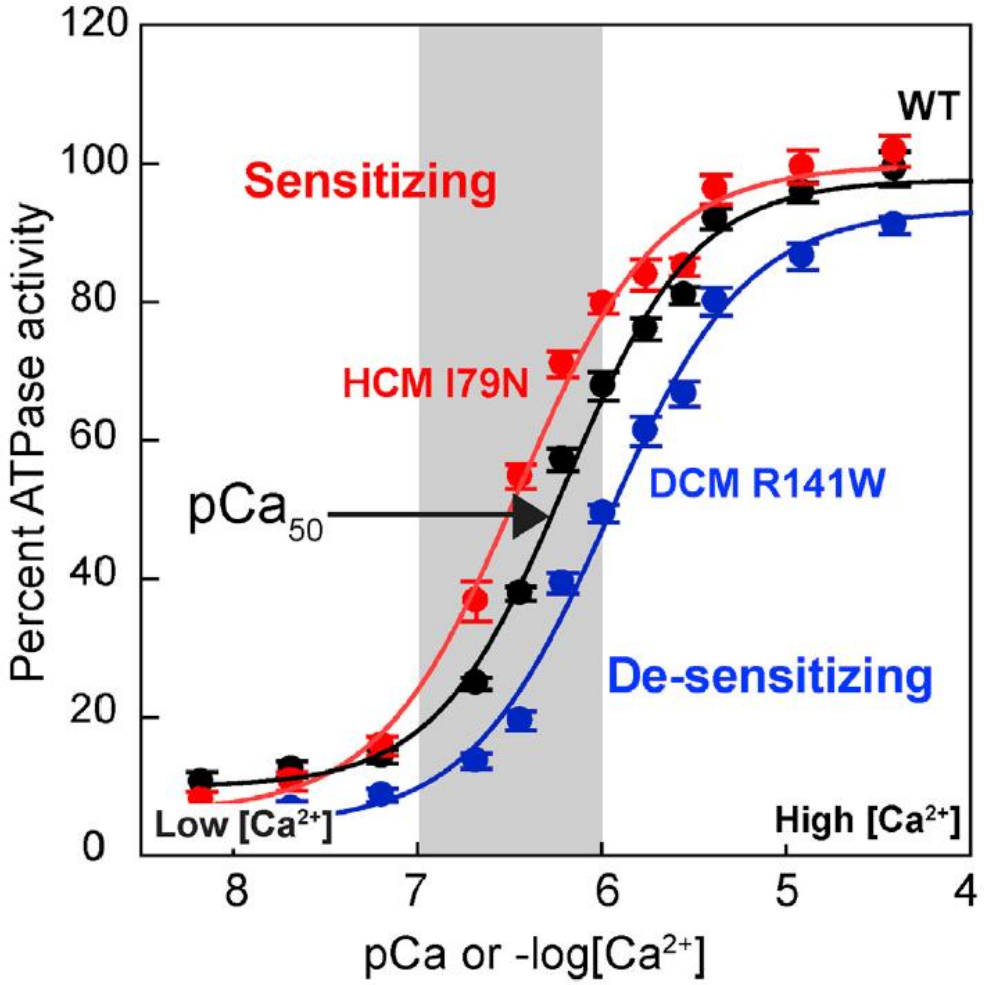


FIGURE 6 In vitro motility taken to the single-molecule level. (*a*) Myosin-coated surfaces drive the movement of fluorescently-labeled actin filaments at velocities comparable to those of muscle contraction (85). (*b*) The dual-beam laser-trap assay for measuring nanometer steps and piconewton forces of a single myosin molecule (55). (*c*) Force transients measured by clamping the position of the actin-bound polystyrene bead on the left (*purple*, in panel *b*) as the myosin is trying to move the actin to the right. (*d*) Mean intrinsic forces from multiple preparations of wild-type human β-cardiac myosin S1 (*black circles*) and human β-cardiac myosin S1 carrying the HCM-causing mutation R453C (*red circles*) (49). To see this figure in color, go online.

James A. Spudich

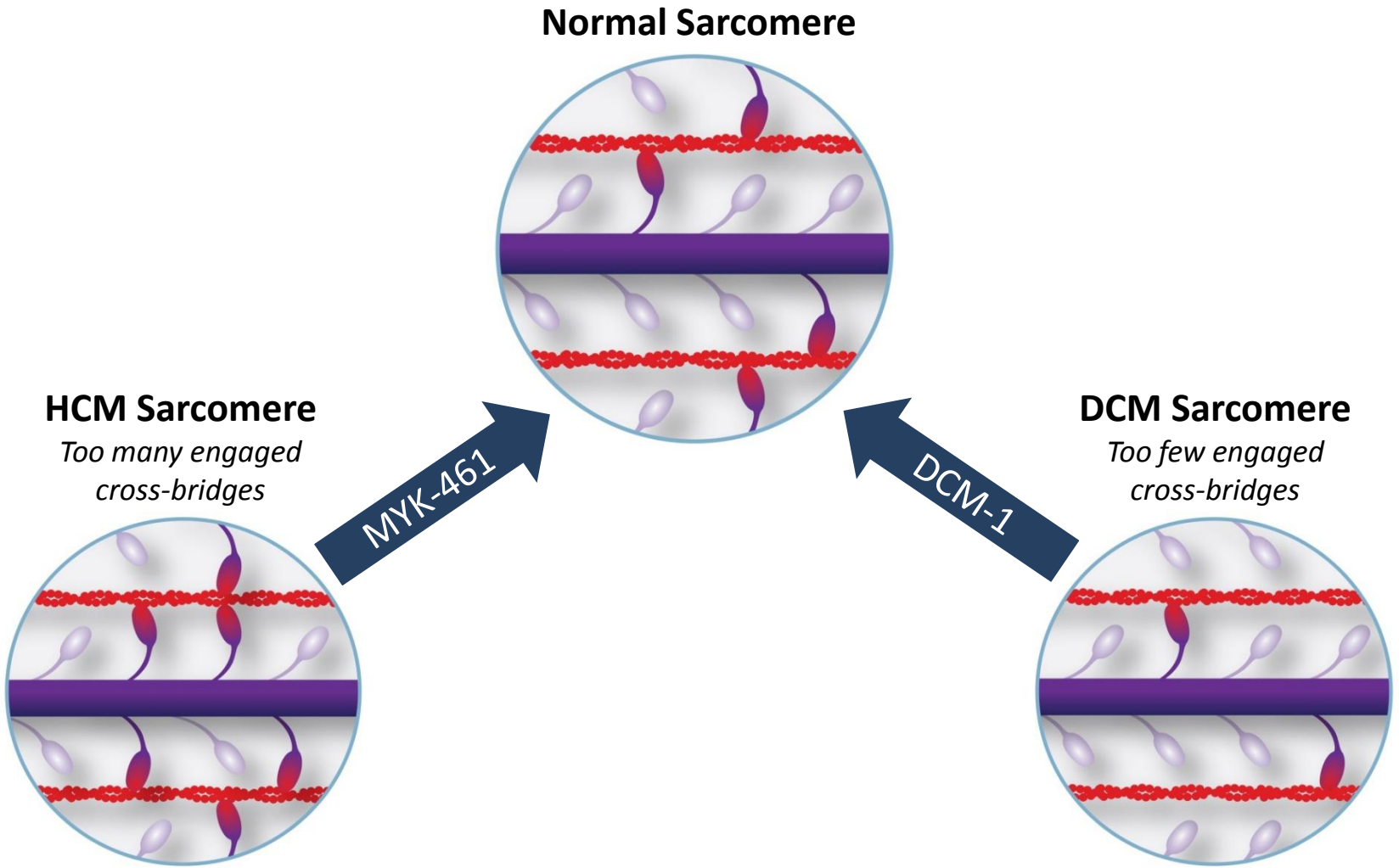
Biophysical Journal Volume 106 March 2014 1236–1249



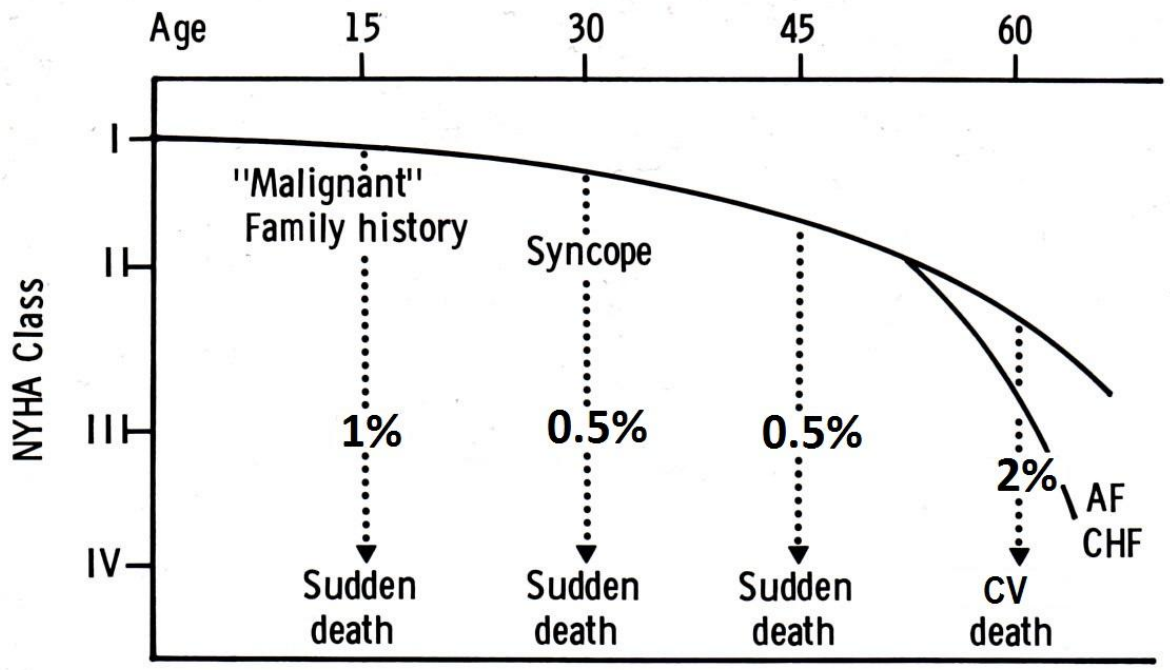
James A. Spudich

Biophysical Journal Volume 106 March 2014 1236–1249

Overview of MyoKardia Program: Product Candidates Designed to Correct the Underlying Causal Defects

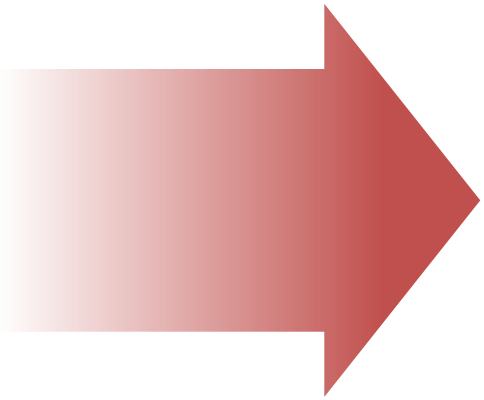


Natural History of HCM circa 2014



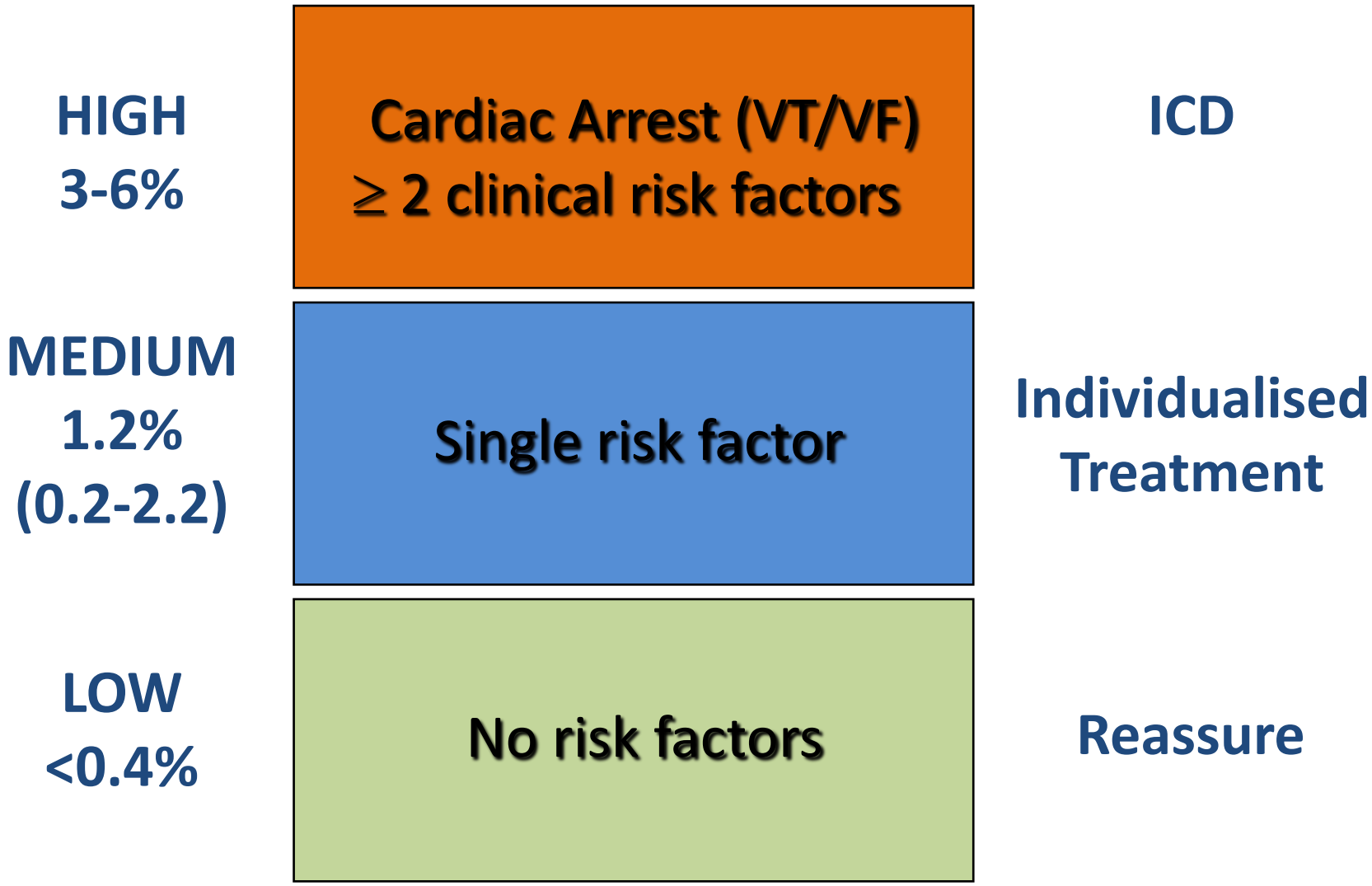
Risk Factors in HCM

Youth
Genotype
Family history
Exercise capacity
Syncope
Severe LVH
Large gradient
Diastolic dysfunction
Abn exercise BP
Ischemia
Atrial fibrillation
Non-sustained VT
Inducible VT / VF
Fractionation



Family history
Syncope
Exercise BP
NSVT
LVH

Sudden Death Risk in HCM



SCD Risk Predictors in HCM

Predictor variable	**SCD risk prediction model**	
	Hazard Ratio (95% Confidence Interval)	**p**
Age (years)	0.98 (0.97, 0.99)	0.001
Maximal wall thickness (mm)	1.17 (1.01, 1.37)	0.042
Maximal wall thickness^2 (mm^2)	0.997 (0.99, 1.0003)	0.078
Left atrial diameter (mm)	1.03 (1.01, 1.05)	0.006
LV outflow gradient (mmHg)	1.004 (1.001, 1.01)	0.021
Family History SCD	1.58 (1.18, 2.13)	0.002
NSVT	2.29 (1.64, 3.18)	<0.001
Unexplained syncope	2.05 (1.48, 2.82)	<0.001

O'Mahony et al, EHJ 2013

Absolute Risk Assessment in HCM

Age and NSVT

	Pt characteristic
Age	17
MWT	23
LA	44
LVOTO	64
FHSCD	0
NSVT	1
Syncope	0
PI	3.99
Survival	0.897431905
SCD at 5y	10.25680946

	Pt characteristic
Age	58
MWT	23
LA	44
LVOTO	64
FHSCD	0
NSVT	1
Syncope	0
PI	3.252
Survival	0.94957981
SCD at 5y	5.042018989

Age and LVH

	Pt characteristic
Age	50
MWT	23
LA	44
LVOTO	64
FHSCD	0
NSVT	0
Syncope	0
PI	2.57
Survival	0.974181337
SCD at 5y	2.581866337

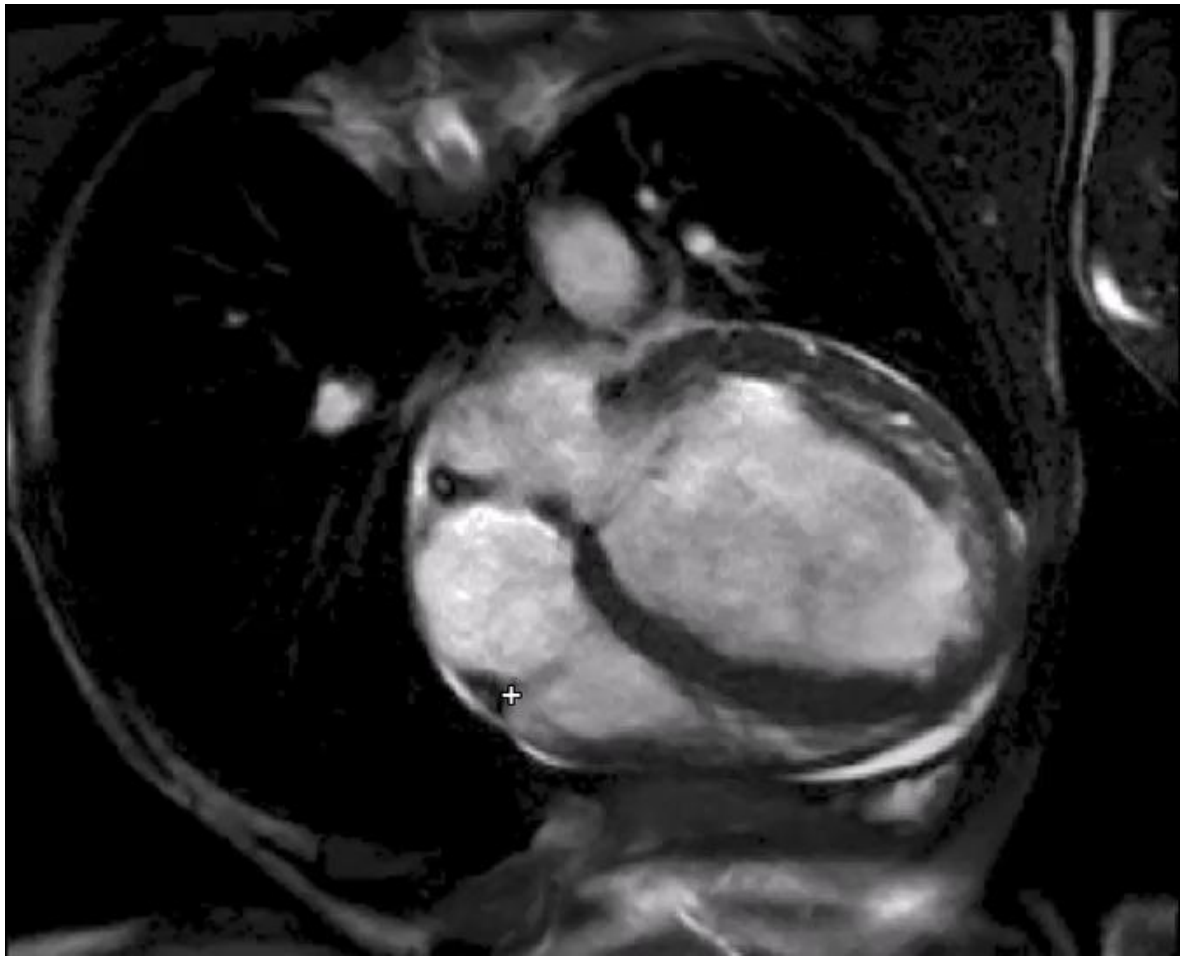
	Pt characteristic
Age	50
MWT	33
LA	44
LVOTO	64
FHSCD	0
NSVT	0
Syncope	0
PI	2.48
Survival	0.976377052
SCD at 5y	2.362294786

	Pt characteristic
Age	17
MWT	33
LA	44
LVOTO	64
FHSCD	0
NSVT	0
Syncope	0
PI	3.074
Survival	0.957624251
SCD at 5y	4.237574868

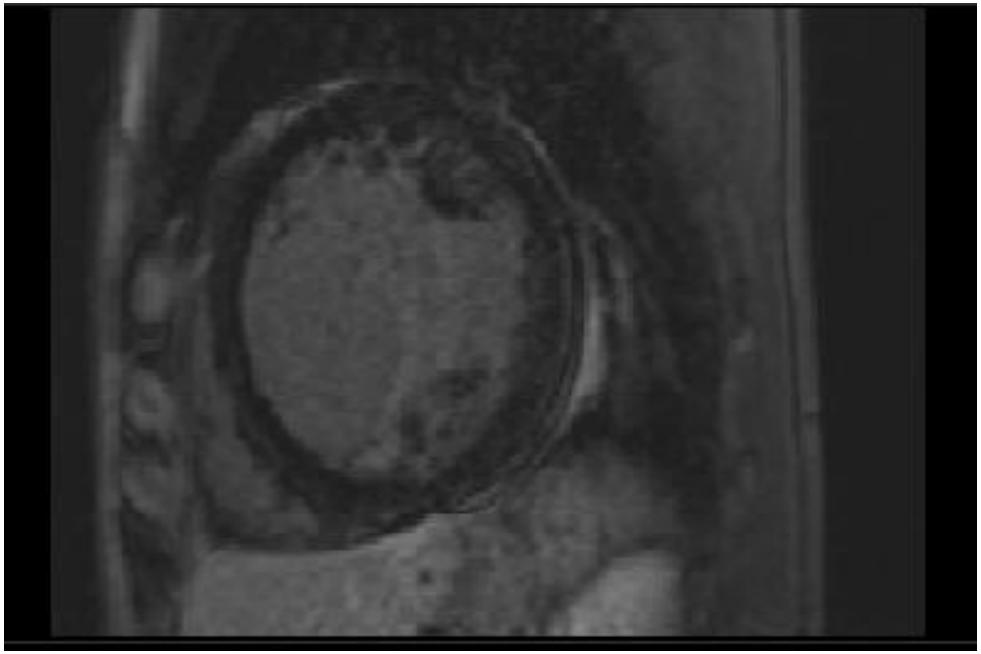
$$\hat{P}_{SCD\,at\,5\,years} = 1 - 0.998^{\exp(\text{Prognostic Index})}$$

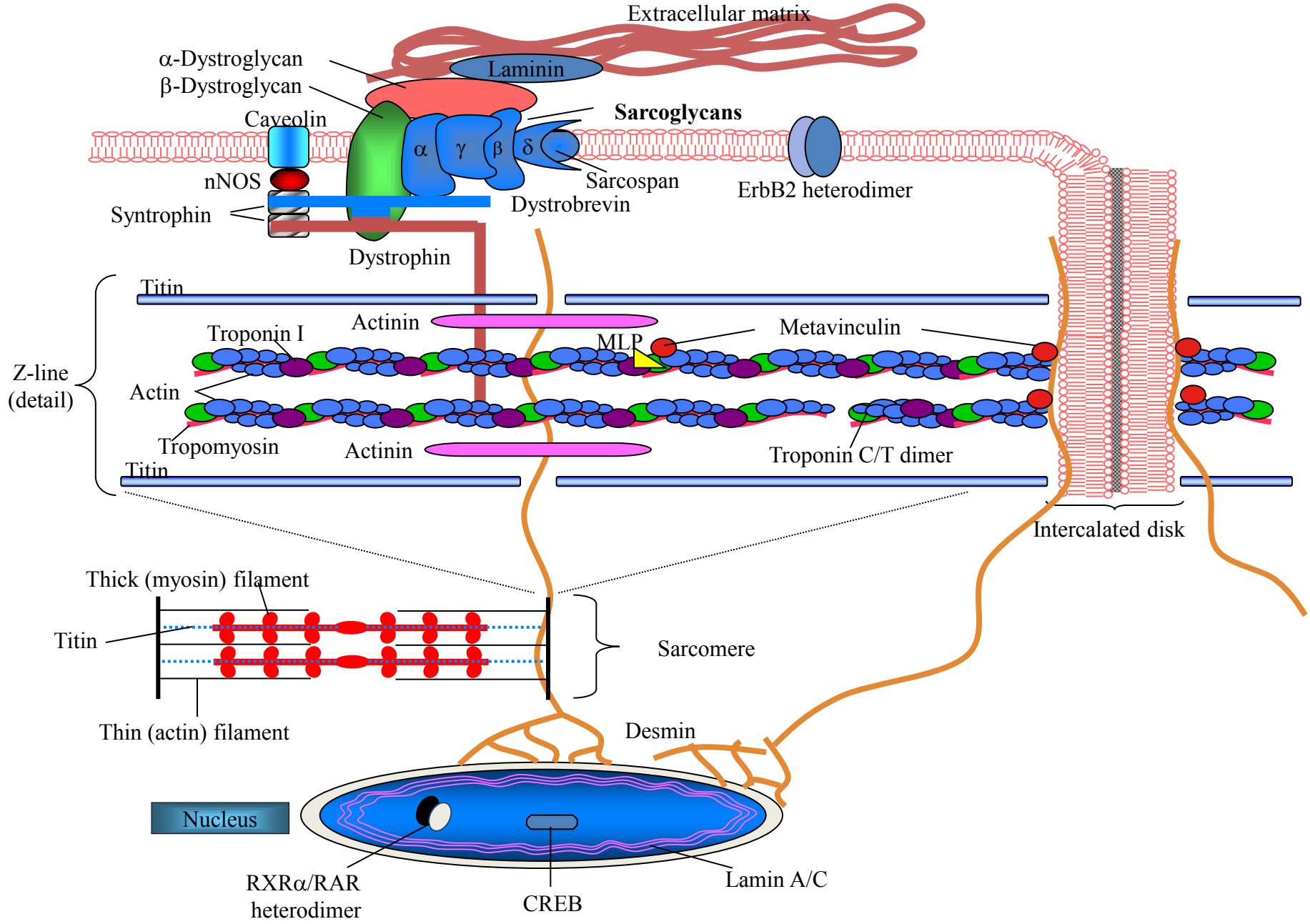
http://doc2do.com/hcm/webHCM.html

DCM

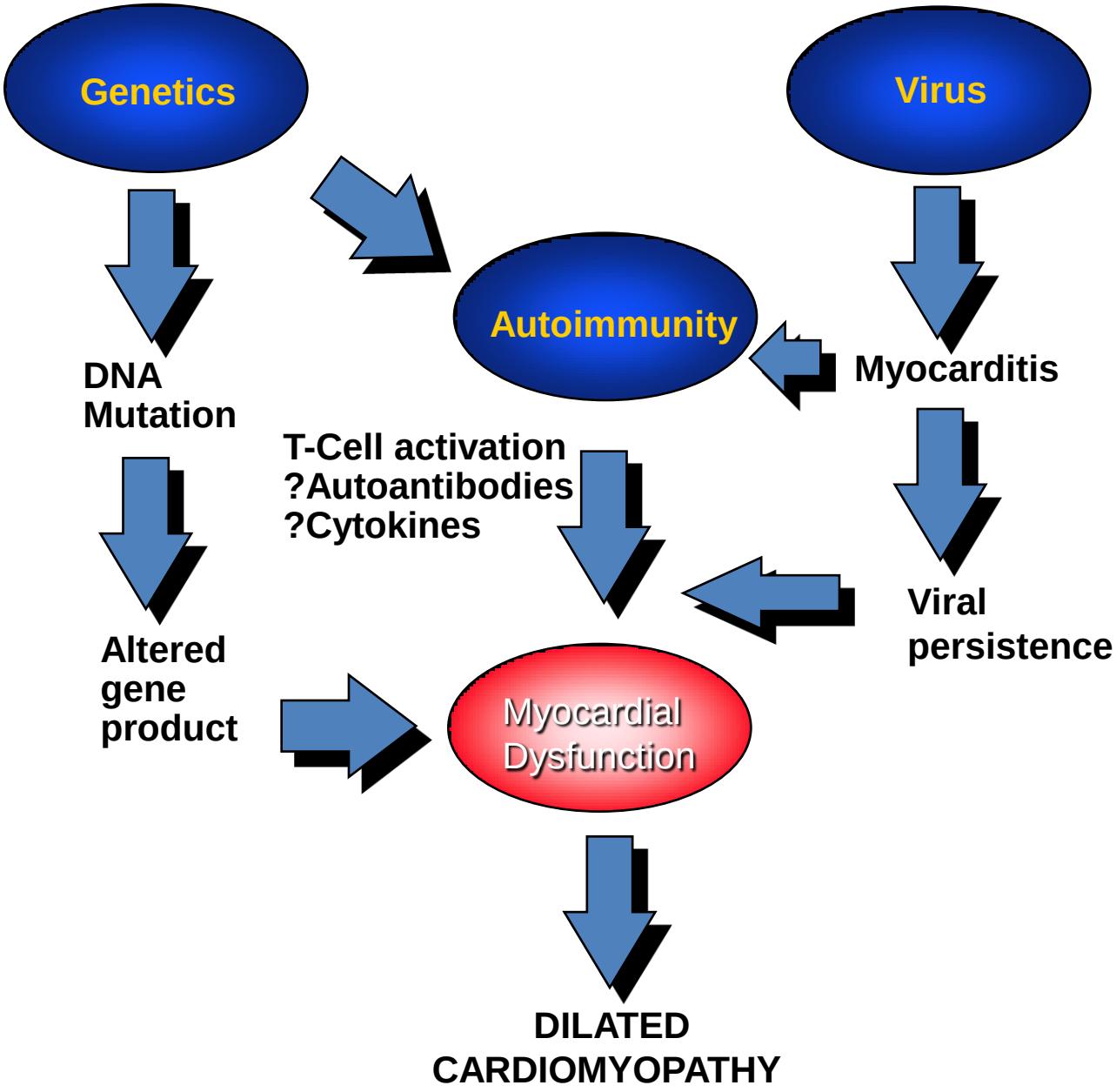


DCM



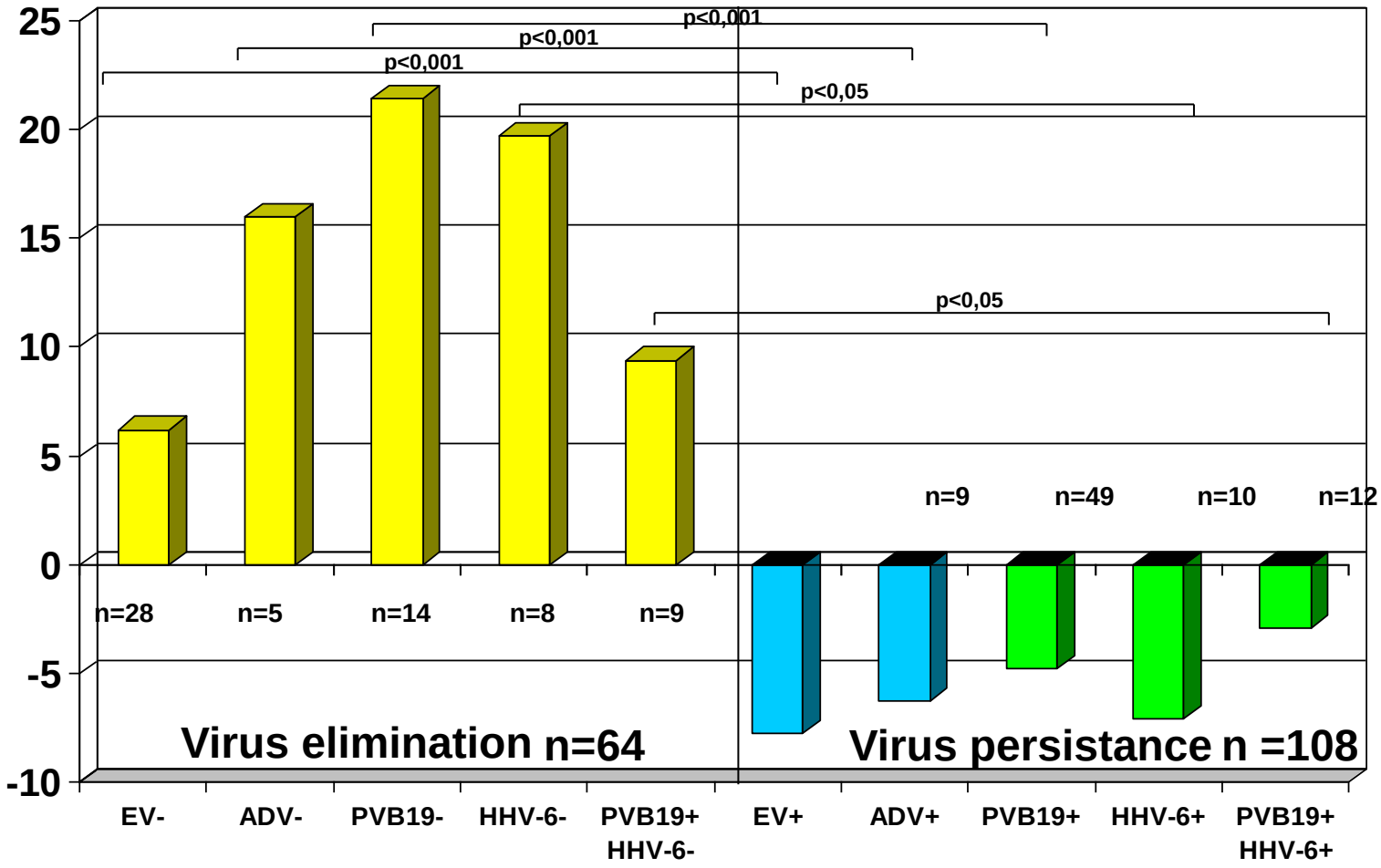


Modified from J. Towbin



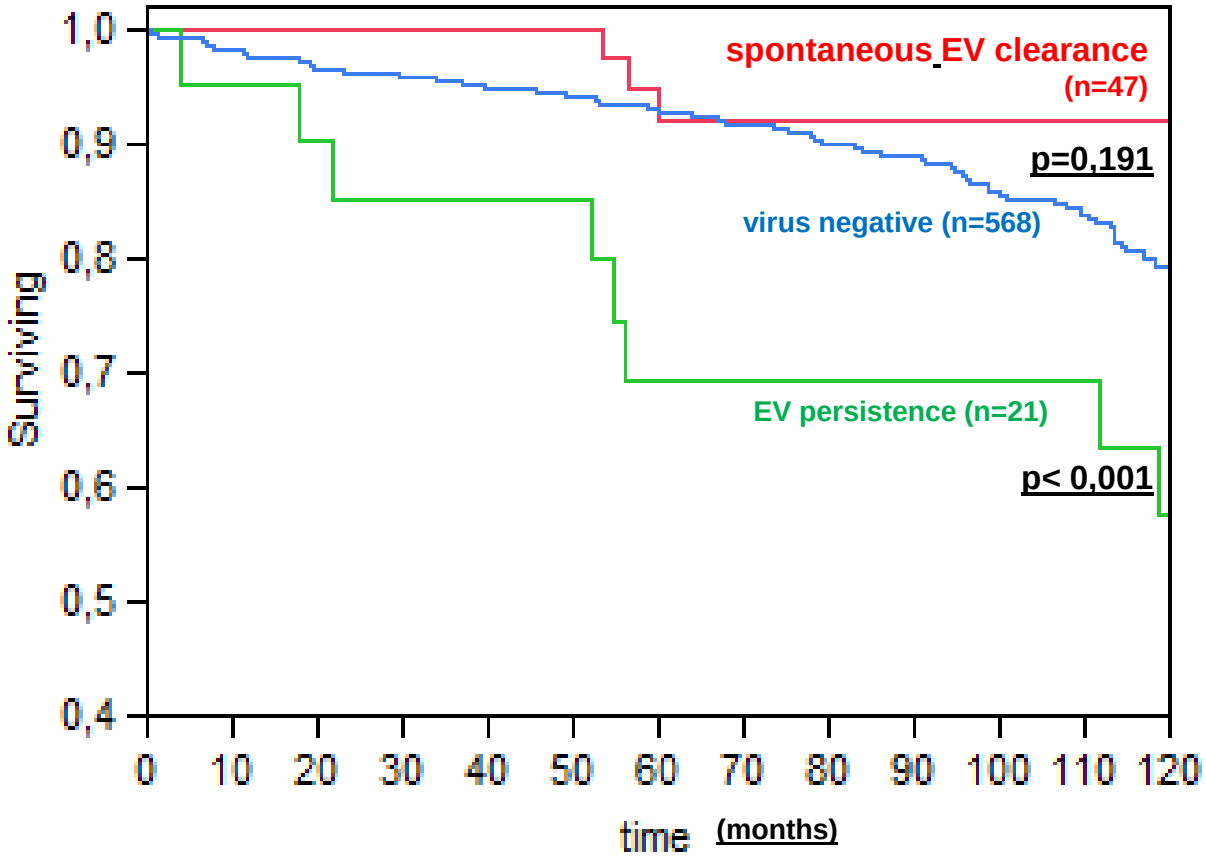
Adapted from Mestroni et al BHJ 1997;72:S35

The spontaneous and chronic course (8 months) of cardiac viral infections determines the clinical course of the disease



Long-term outcome – 10 year survival

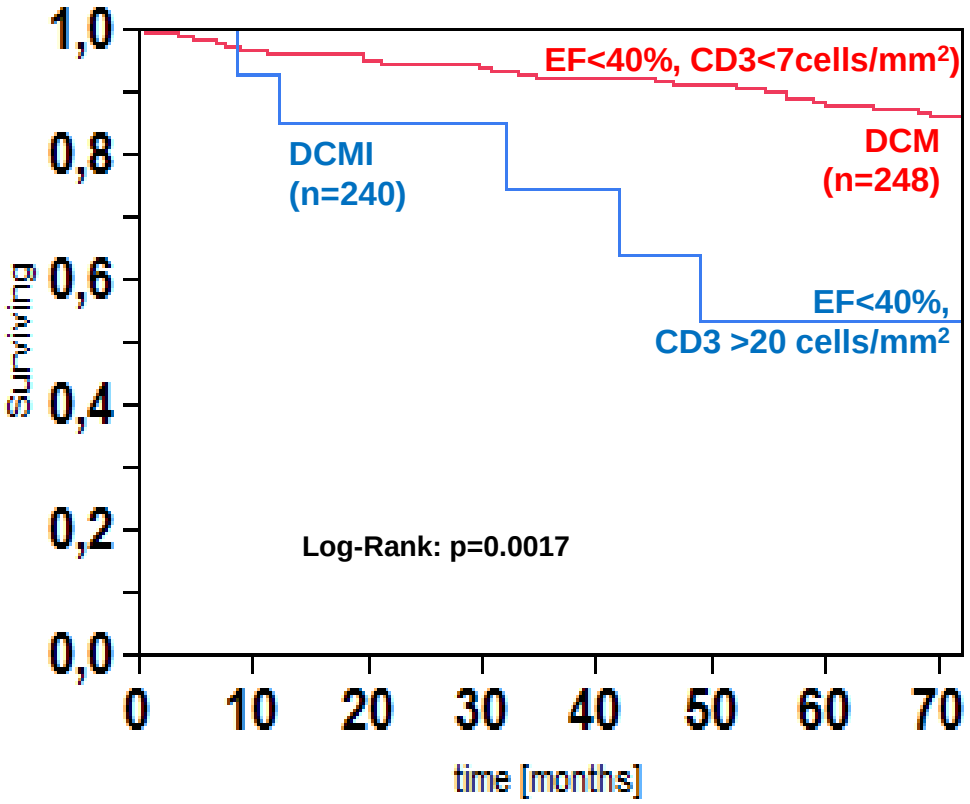
- enterovirus positive vs virus negative DCM – patients



Kühl U, Schultheiss HP et al. JACC, 2012

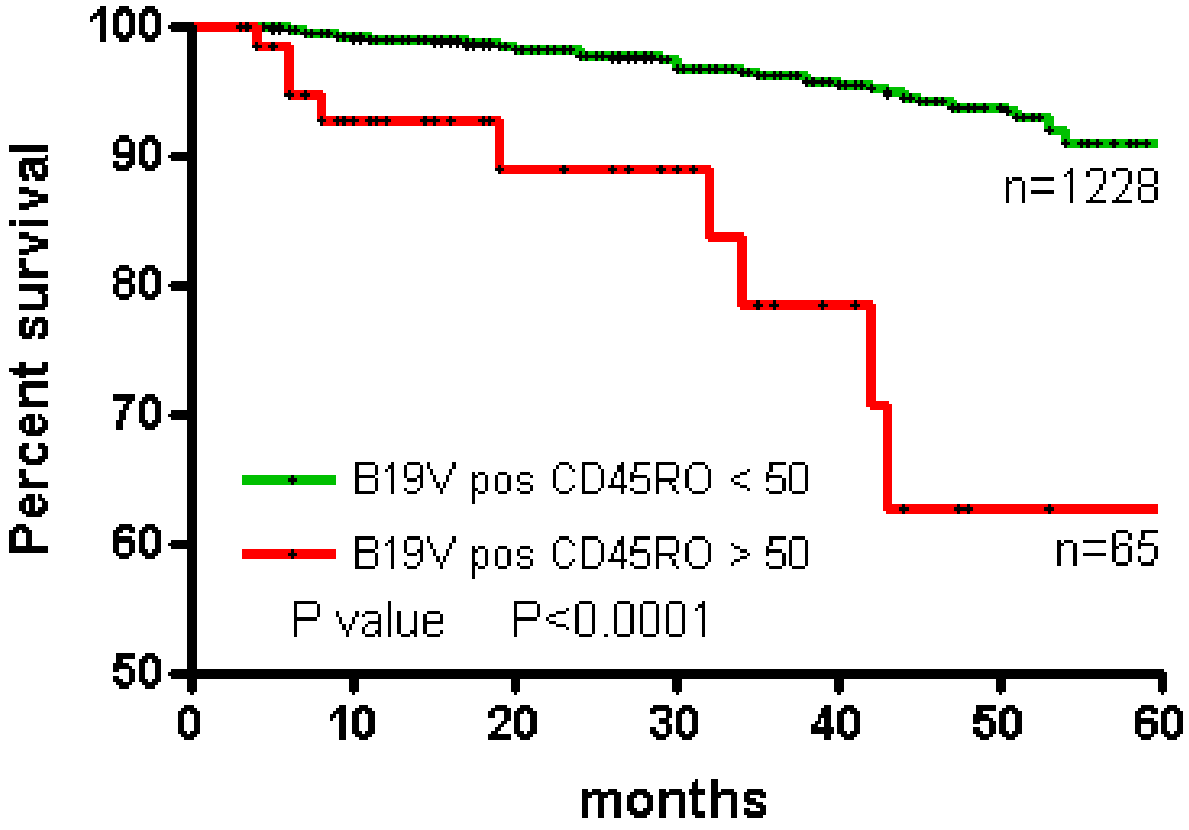
EMB-based inflammation predicts poor outcome in patients with suspected myocarditis

6 year mortality rate of virus-negative patients with DCM vs. DCMI (EF < 40% , CD3 >20 or <7cells/mm2)

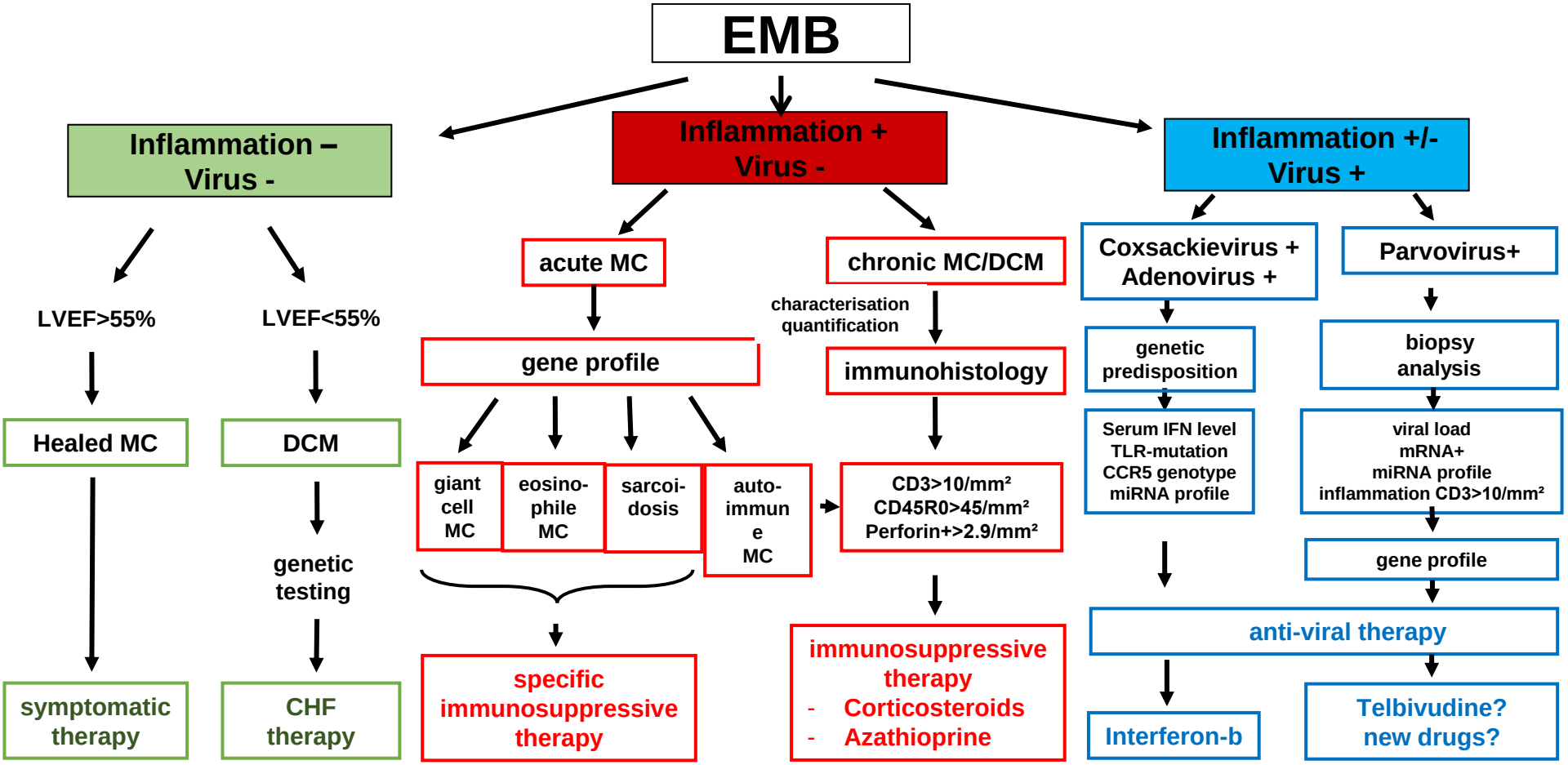


Kühl, U, Schultheiss, HP et al , submitted

Survival in B19V positive patients with MC or DCM (CD45RO pos. cells)



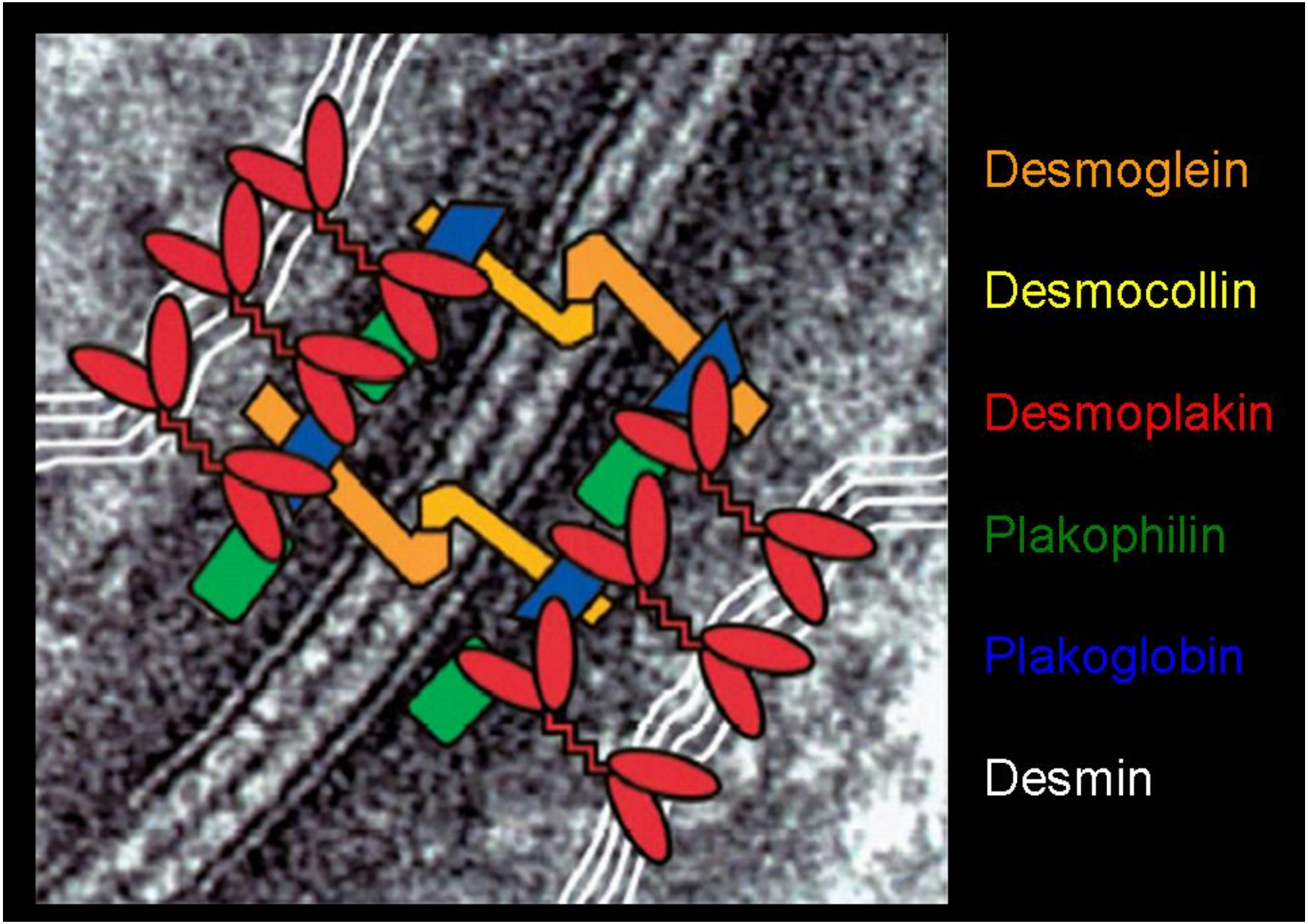
Acute/Chronic Myocarditis: Personalized Medicine



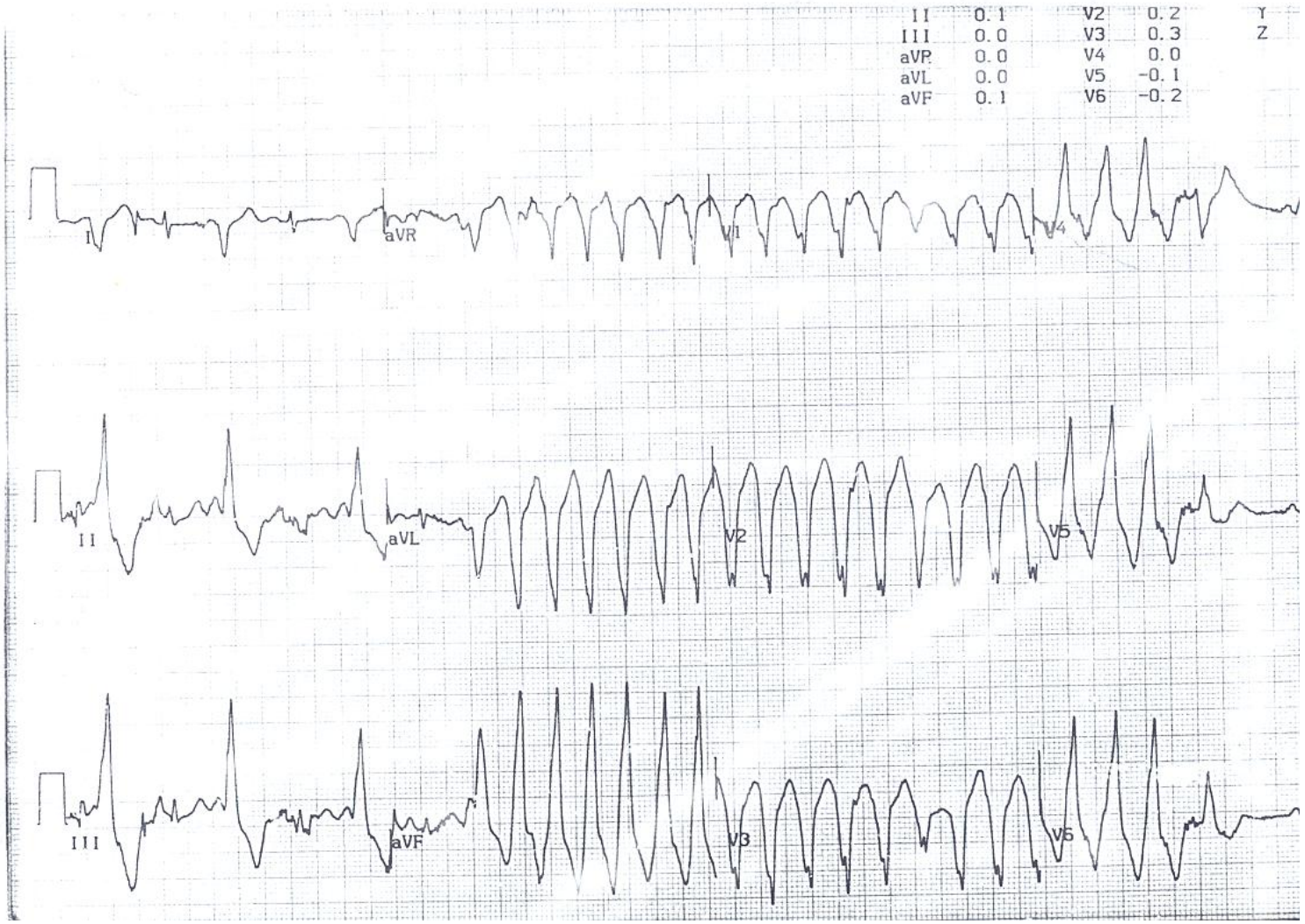
Institute of Cardiac Diagnostics and Therapy (IKDT)- Berlin, Germany

Prof. Heinz-Peter Schultheiss

Arrhythmogenic Cardiomyopathy

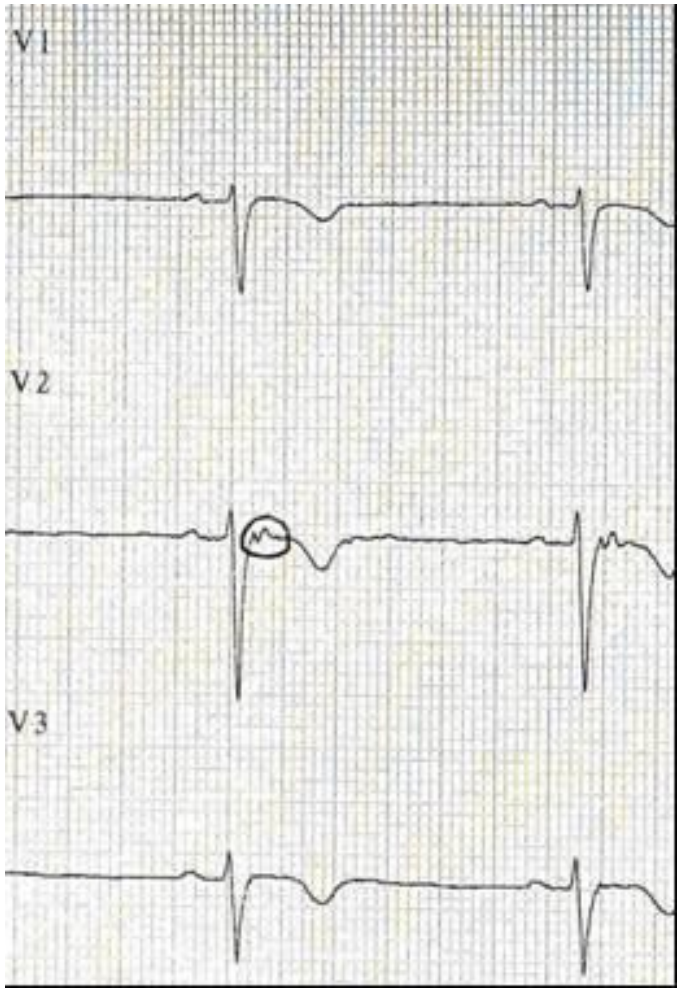


ARVC Exercise: LBBB VT

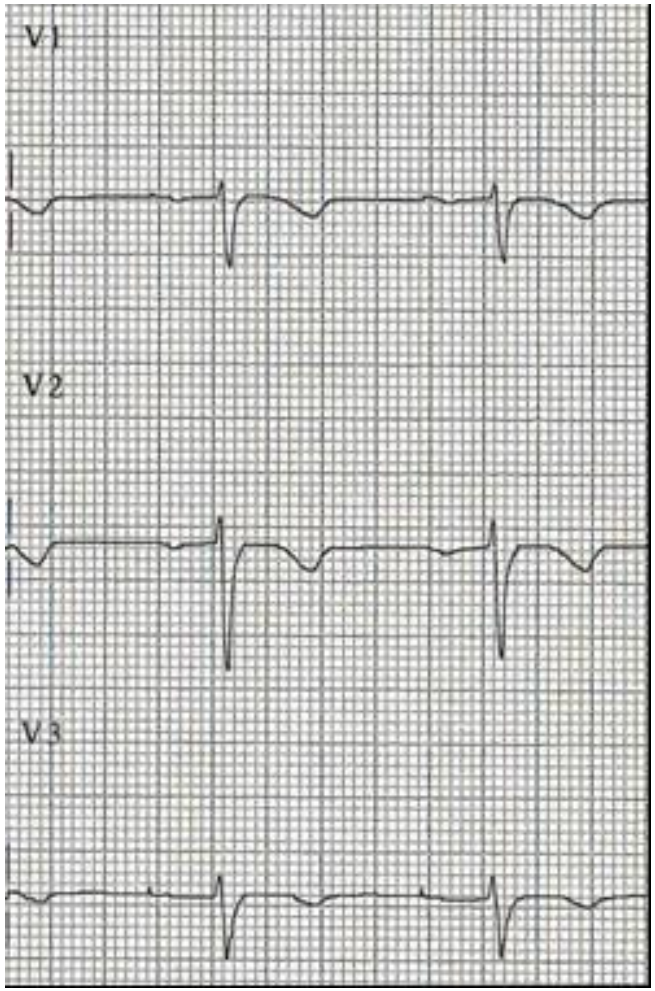


ARVC

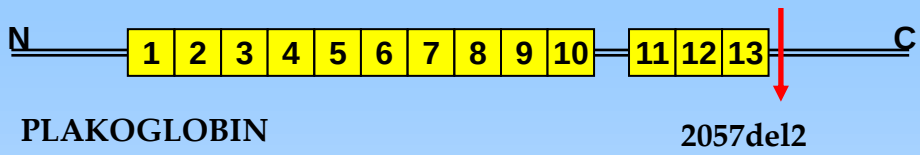
12/11/2003

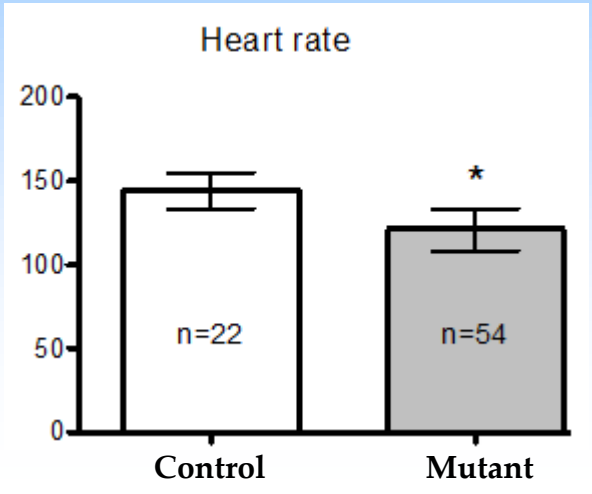


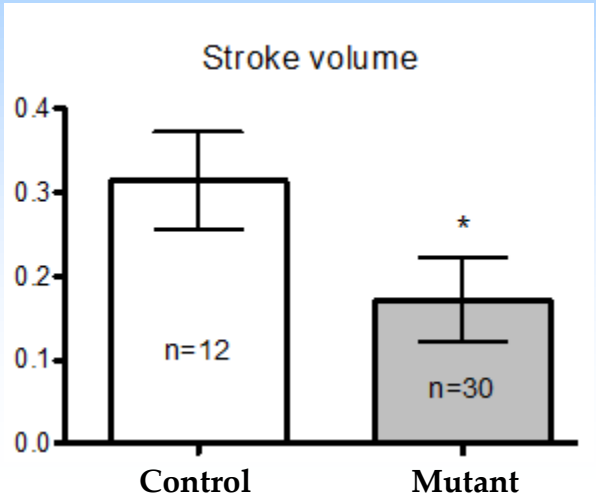
02/02/2005

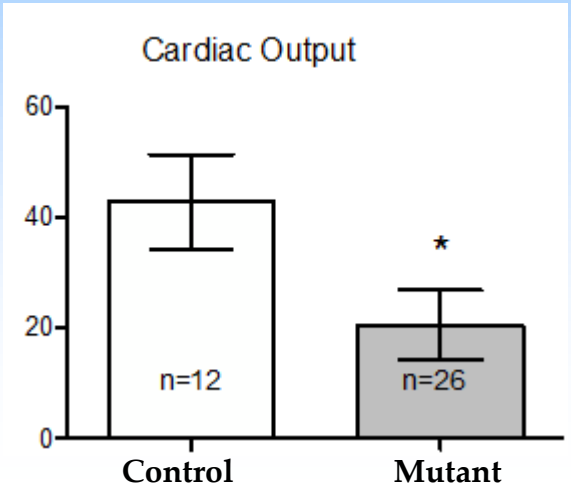


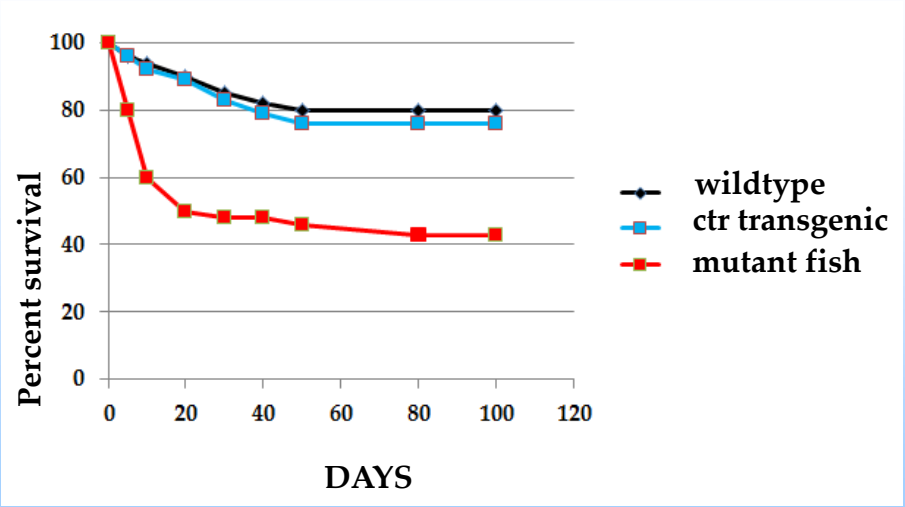
A Small Fish with a Big Heart…

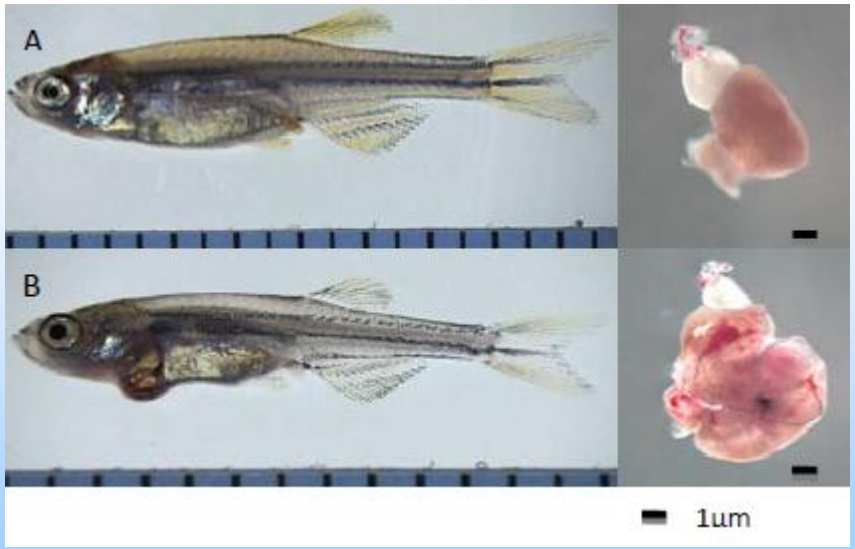








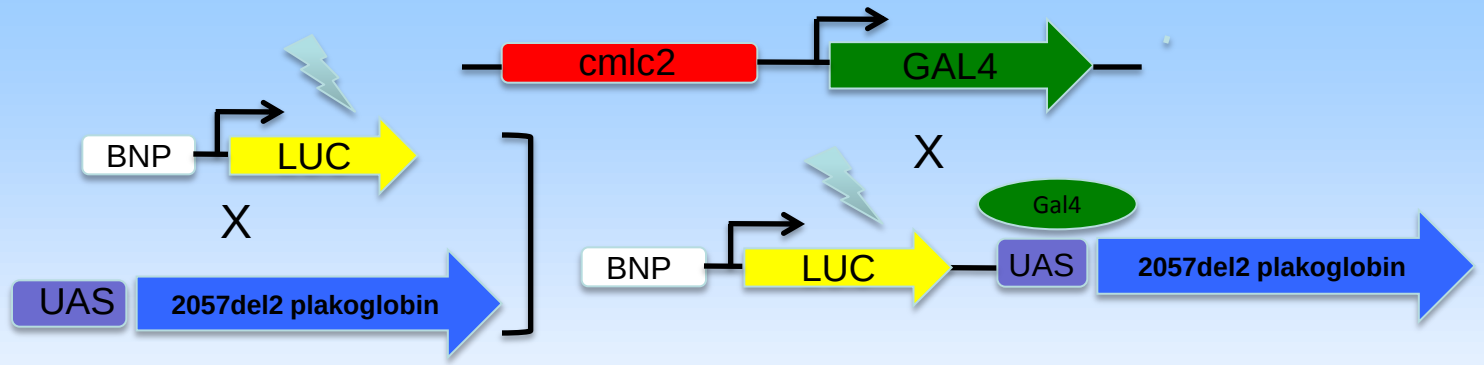


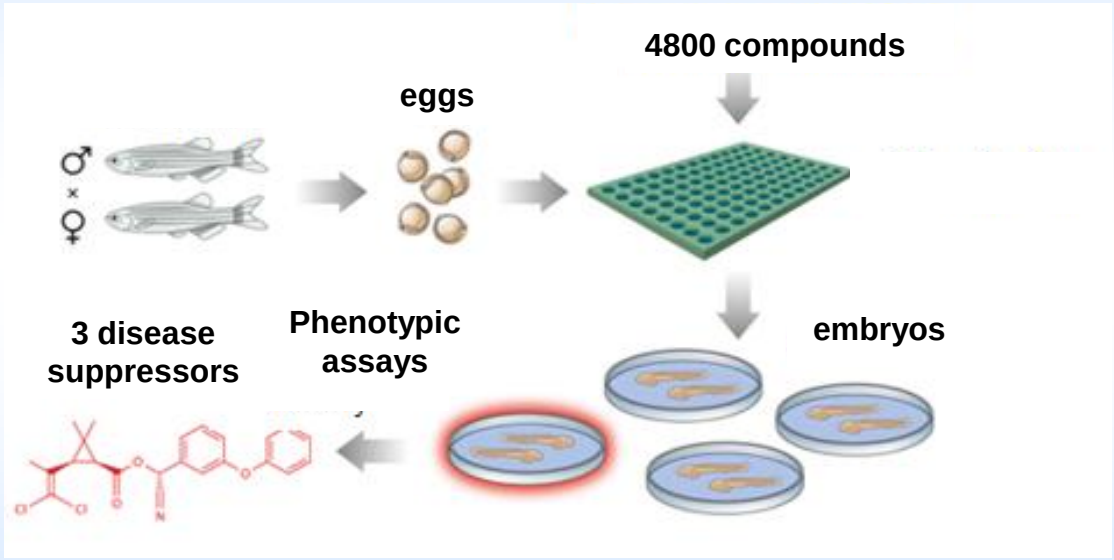


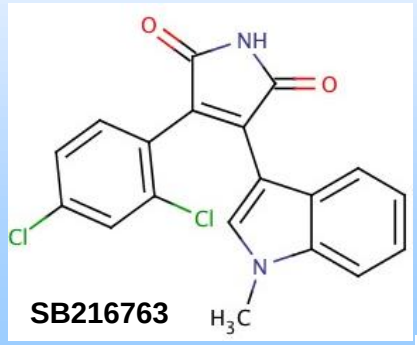
5-week control sibling (A) and mutant (B) and their hearts

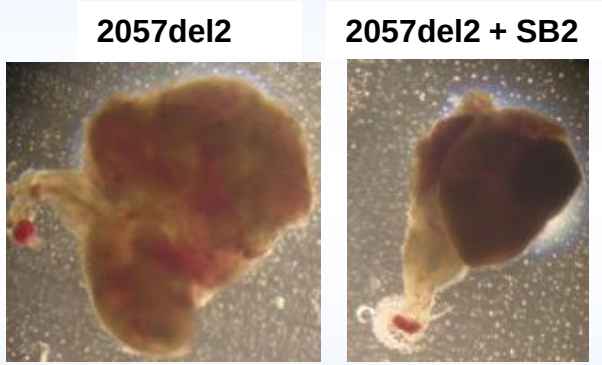
Sci Transl Med. 2014 June 11; 6(240): 240ra74.

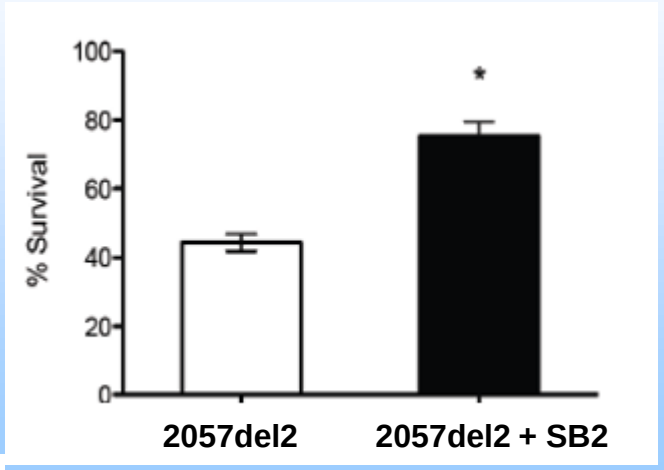
High-Throughput Library Screening…







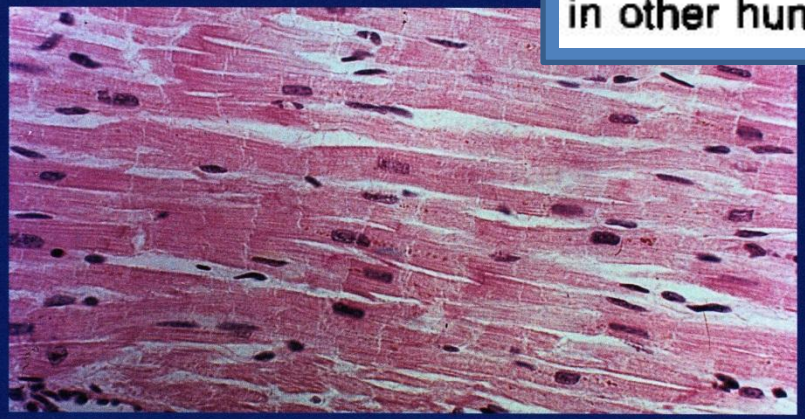


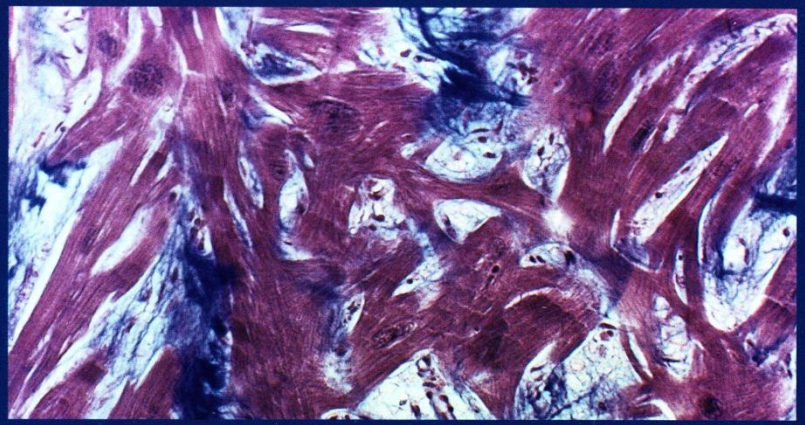


Sci Transl Med. 2014 June 11; 6(240): 240ra74.

Cell

Volume 62 Number 5 September 7, 1990





Mutations in Myosin Heavy Chain Responsible for Familial Hypertrophic Cardiomyopathy

Understanding the mechanism by which mutations in the cardiac MHC genes produce the pathology characteristic of FHC may elucidate a molecular basis for myocyte growth and development and provide new insights into how these are altered in other human diseases.

Summary

– on the path, but progress to biologically based personalized care is slow