HEART FAILURE:
GENETIC DEFECTS IN THE MOLECULAR MOTORS THAT POWER THE HEART

David M. Warshaw, Ph.D.
Molecular Physiology & Biophysics

Myosin Molecular Motor
Genetic Defects in Myosin Motor

Hank Gathers
Reggie Lewis

Leading cause of sudden death in young adults.

1 in 200 people have genetic defect (3,100 Vermonters)
Familial Hypertrophic Cardiomyopathy (FHC)  
Normal  
Dilated Cardiomyopathy (DCM)

Seidman and Seidman Cell (2001)
Myosin Genetic Mutations

R403Q  →  S532P

2000 amino acids

● Hypertrophic

● Dilated

http://genetics.med.harvard.edu/~seidman/cg3/HCM_DCM_myo
$\text{Power} = \text{Force} \times \text{Velocity}$

Myosin Molecular Motor
Heart

Cell

Sarcomere

Actin
Myosin
Motility Assay

Actin Filament Velocity $\sim$ Muscle Velocity

http://motility.york.ac.uk/
Star Trek Tractor Beam

Laser Trap
Single Molecule Laser Trap Assay
Laser Trap Assay
Heart is the Ultimate Power Generator!

450 Million Revolutions

3 Billion Beats
Power vs. Force Relation

- **$P_{max}$**
- **FHC R403Q**
- **Normal**
- **DCM S532P**

Graph showing the relationship between force/myosin (pN) and power with different conditions.
Depressed Motor Function  

Enhanced Motor Function

DCM  

FHC

Function
Future Perspectives

1. Genetic Testing or Simple EKGs

2. Precision and Individual Therapeutics:
   - Enhance Myosin Power in Dilated Cardiomyopathy
   - Reduce Myosin Power in Hypertrophic Cardiomyopathy
HEART DISEASE

Throttling back the heart’s molecular motor

A small molecule inhibits mutated forms of myosin that cause cardiac hypertrophy

By David M. Warshaw
University of Vermont