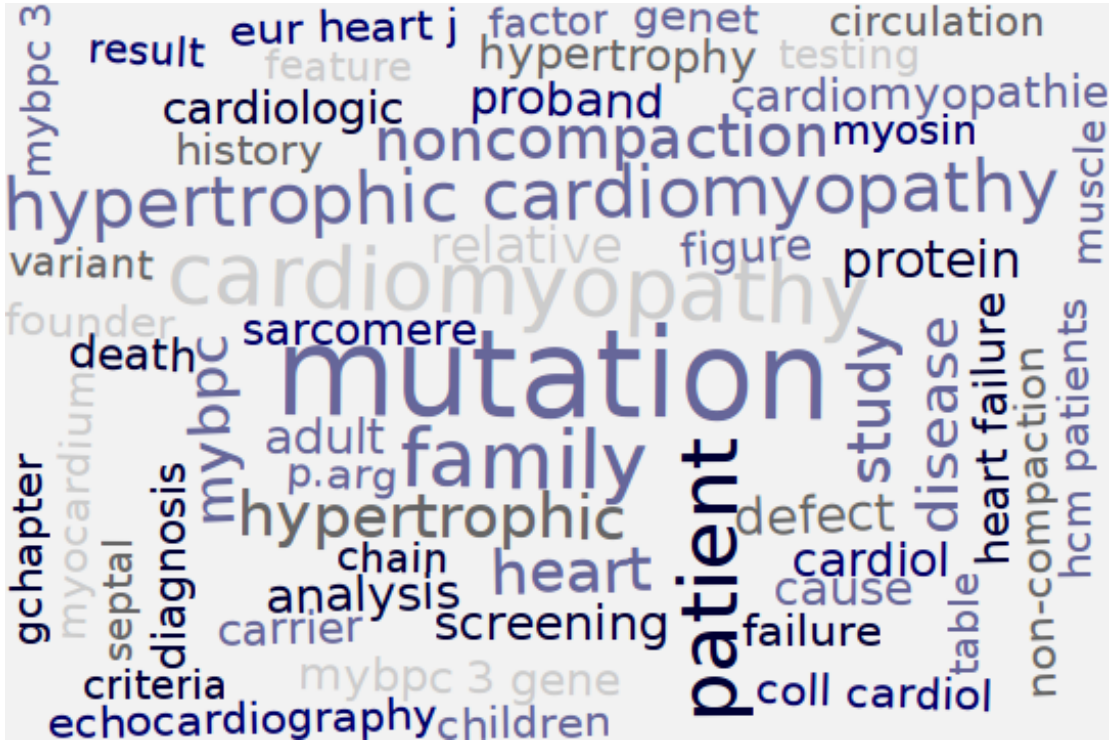
From bench to bedside: the role of science in treating a deadly disease

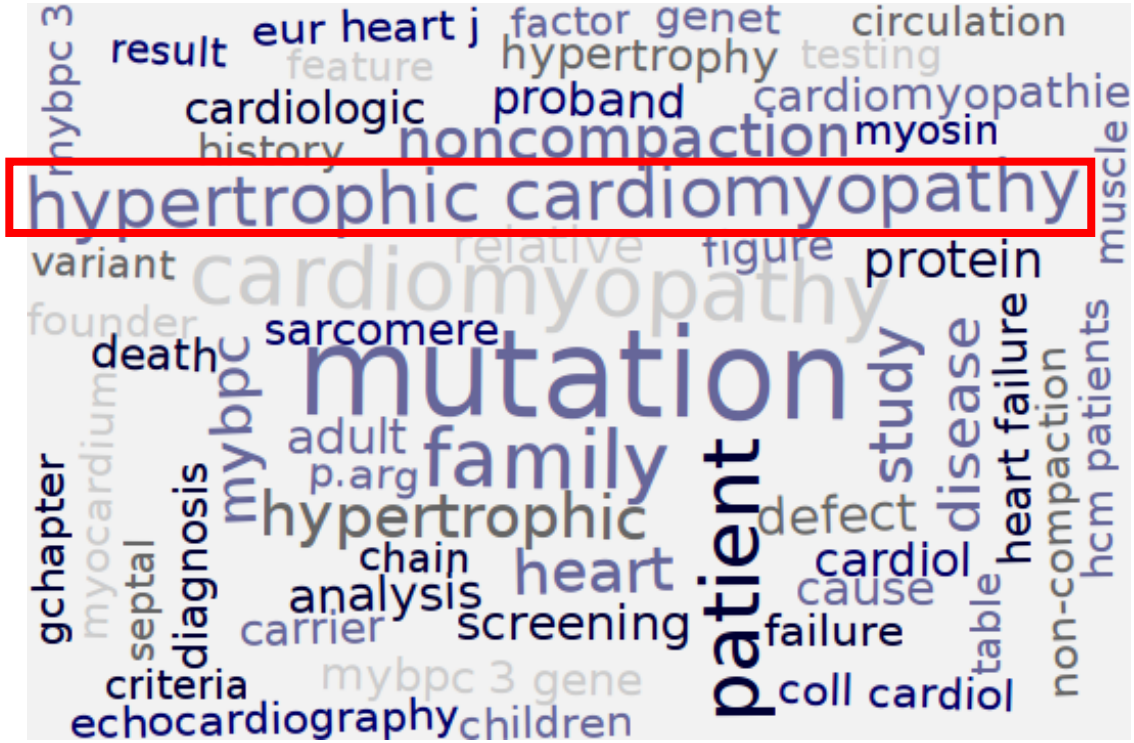
Leslie Leinwand
MCDB and BioFrontiers Institute
University of Colorado, Boulder

Genetic heart disease



As opposed to lifestyle

Genetic heart disease



The most common genetic heart disease is familial hypertrophic cardiomyopathy (HCM)

a.k.a. *a big sick heart that runs in the family*

HCM causes over 30% of sudden deaths in young athletes

Hank Gathers, 23

Reggie Lewis, 27

Damien Nash, 24

A summary of HCM

Mutations in genes that make the heart contract

Incidence: 1/500

Usually people have one normal gene and one mutated gene (has implications for therapy)

No approved therapies; except for a heart transplant or treatment of symptoms

Sex differences (males have worse disease than females at younger ages)

Here is what can happen if someone in your family develops symptoms or dies from HCM:

Your family has the person's DNA screened and finds a mutation that is known to cause the disease

You can choose to get your own DNA screened for the mutation (some parents don't want their children tested)

Let’s say you find out you have the mutation, what do you do?

Sometimes, the first symptom is sudden death

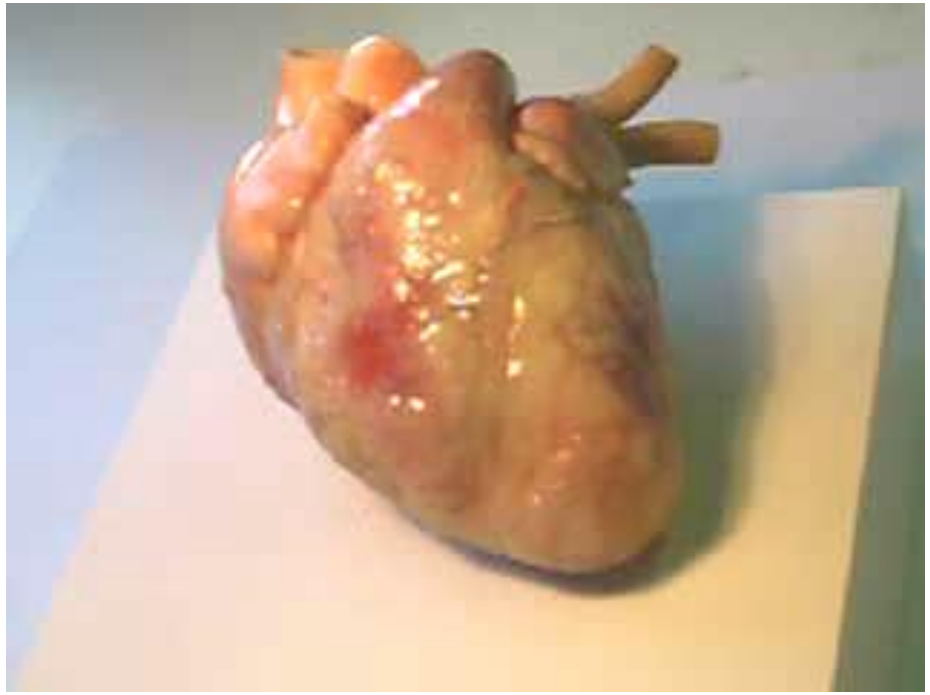
Live a fearful life with frequent testing for an enlarged heart or symptoms

People with the mutant gene are told to lead sedentary lives (even as children)

In order to treat this disease, you have to understand the healthy heart first and then understand the basis for the disease

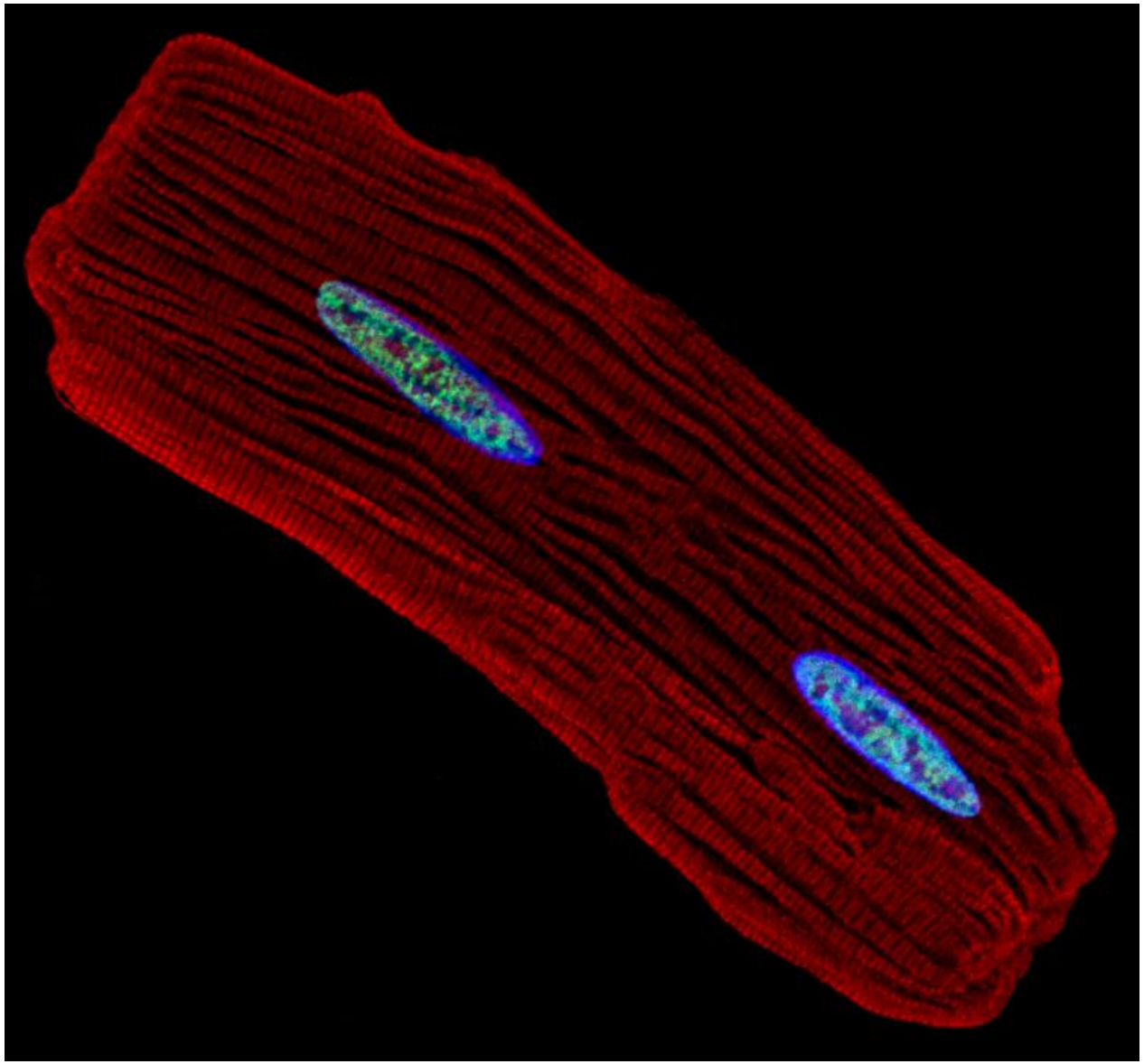
Your heart is a big muscle

- Beats 100,000 times per day
- Pumps blood 12,000 miles per day



Heart cells beat on their own; they don’t need to be in the heart

This is a beautiful single cardiac muscle cell



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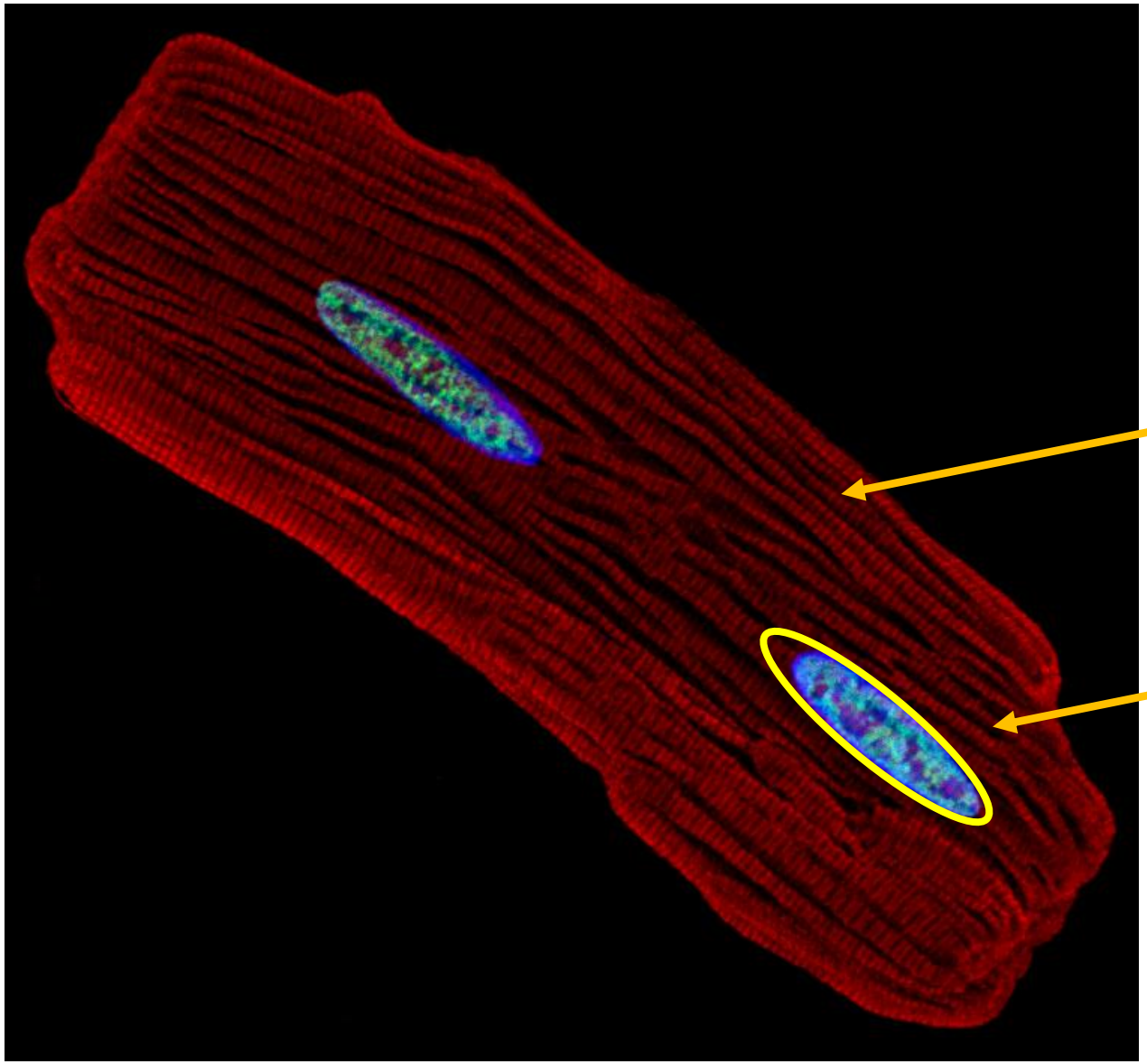
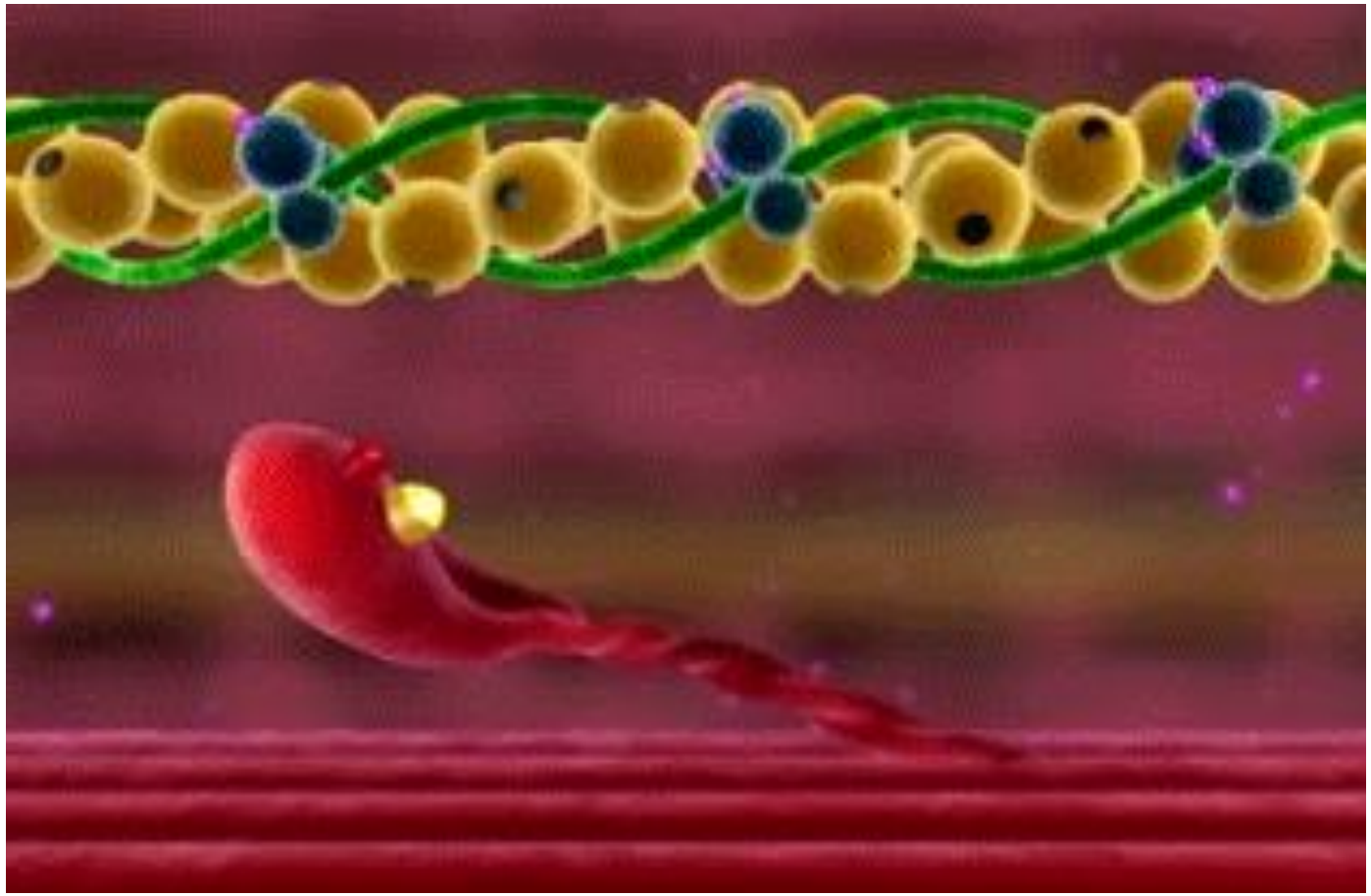


There is a molecular motor called myosin that drives muscle contraction



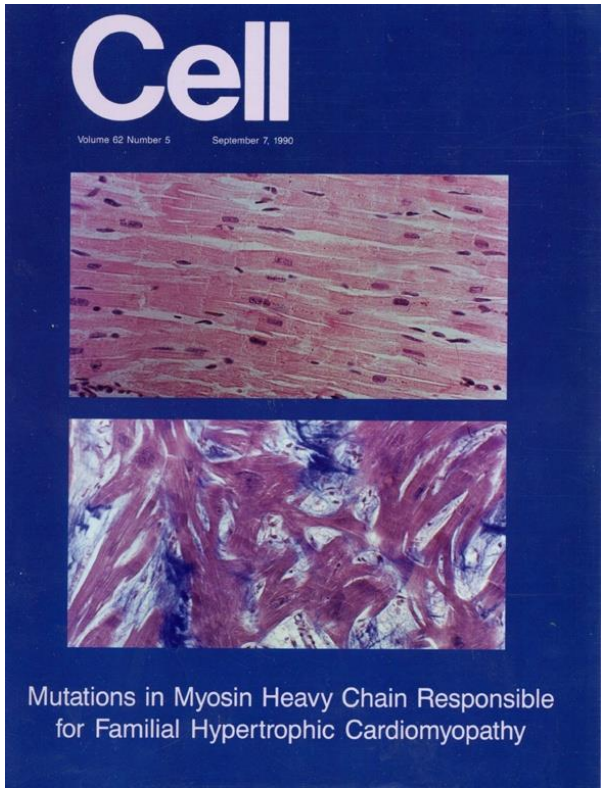
Spudich 2001

A myosin gene mutation was identified that causes HCM in 1990

Cell, Vol. 62, 999–1006, September 7, 1990, Copyright © 1990 by Cell Press

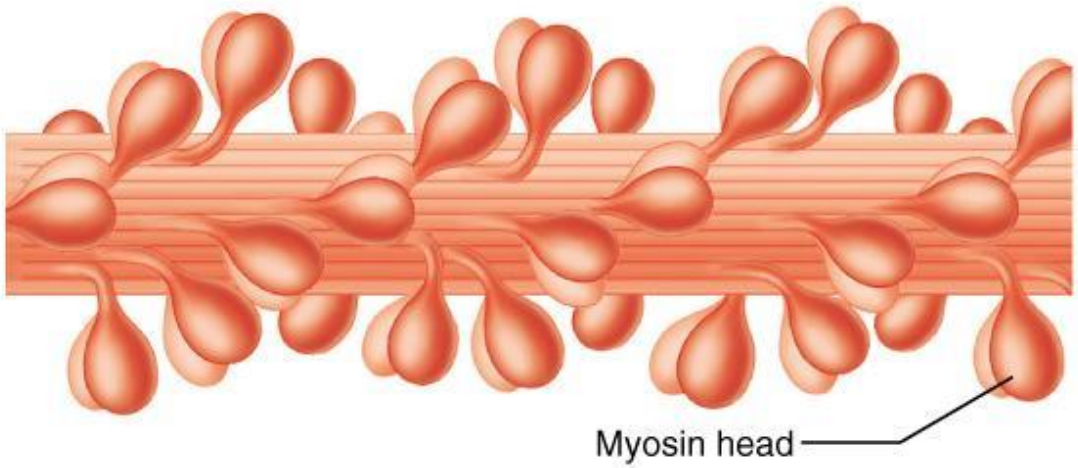
A Molecular Basis for Familial Hypertrophic Cardiomyopathy: A β Cardiac Myosin Heavy Chain Gene Missense Mutation

Anja A. T. Geisterfer-Lowrance,* Susan Kass,† Gary Tanigawa,† Hans-Peter Vosberg,‡ William McKenna,§ Christine E. Seidman,* and J. G. Seidman†



How do these myosin mutations cause disease?

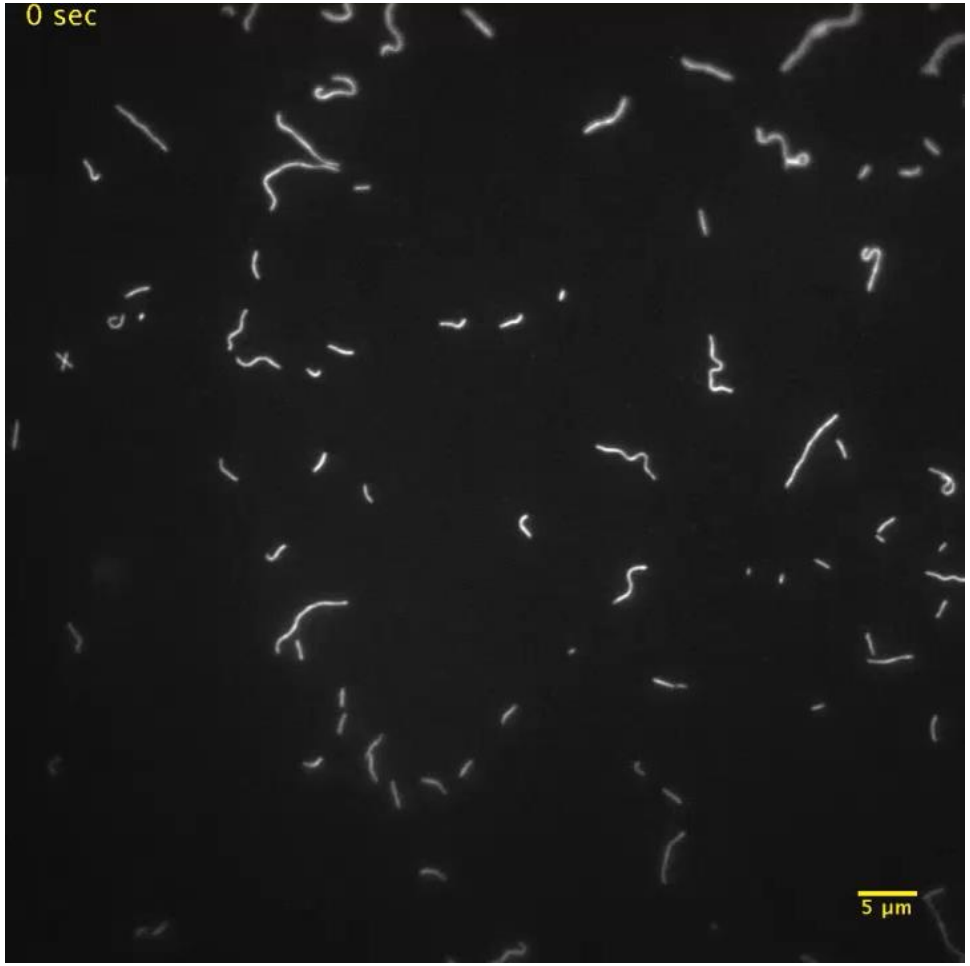
Some mutations likely affect its MOTOR properties

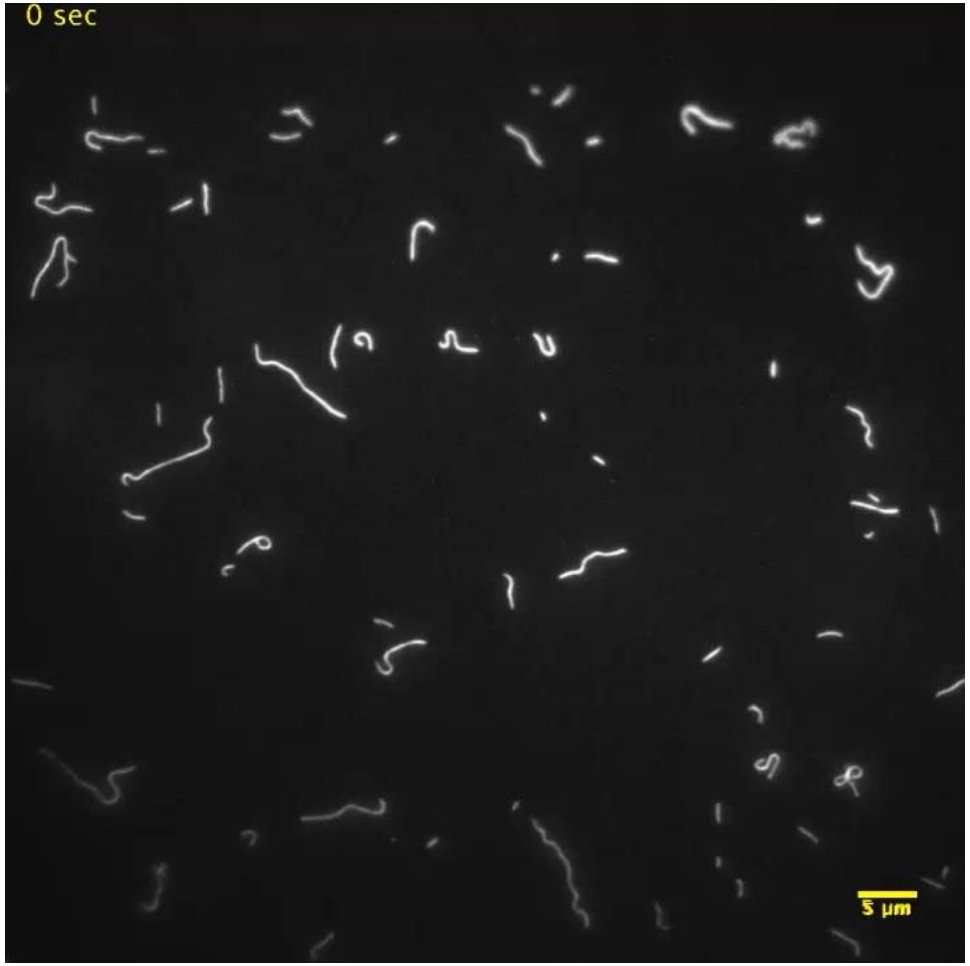


We can measure many aspects of myosin function (both the mutant and non-mutant) since it is one of the best studied proteins in biology.

We can measure the myosin's motor activity under a microscope; watch the myosin moving another part of the muscle machinery and measure their speeds

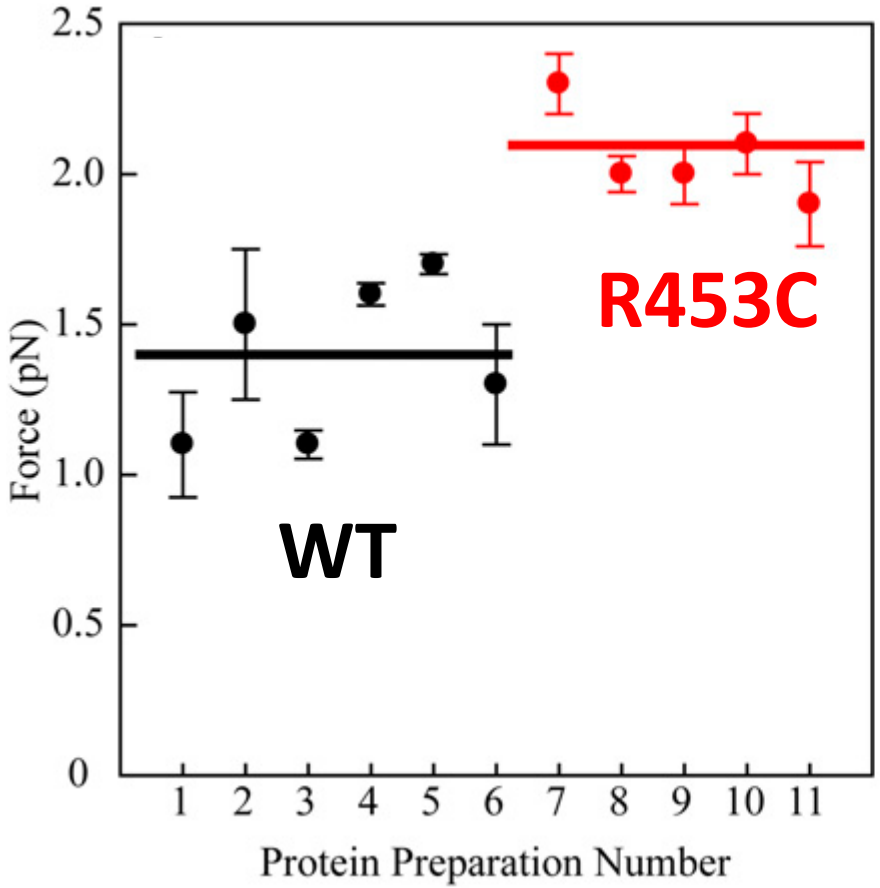
Mutant and normal myosin motors can move at different speeds (can be faster or slower)





Aksel, et al 2015

One mutation in human cardiac myosin produces *increased* force and is thus a *gain-of -function* mutation.



MyoKardia

Founded in 2012, by Leinwand, Seidman, Seidman and Spudich

Went public in 2015

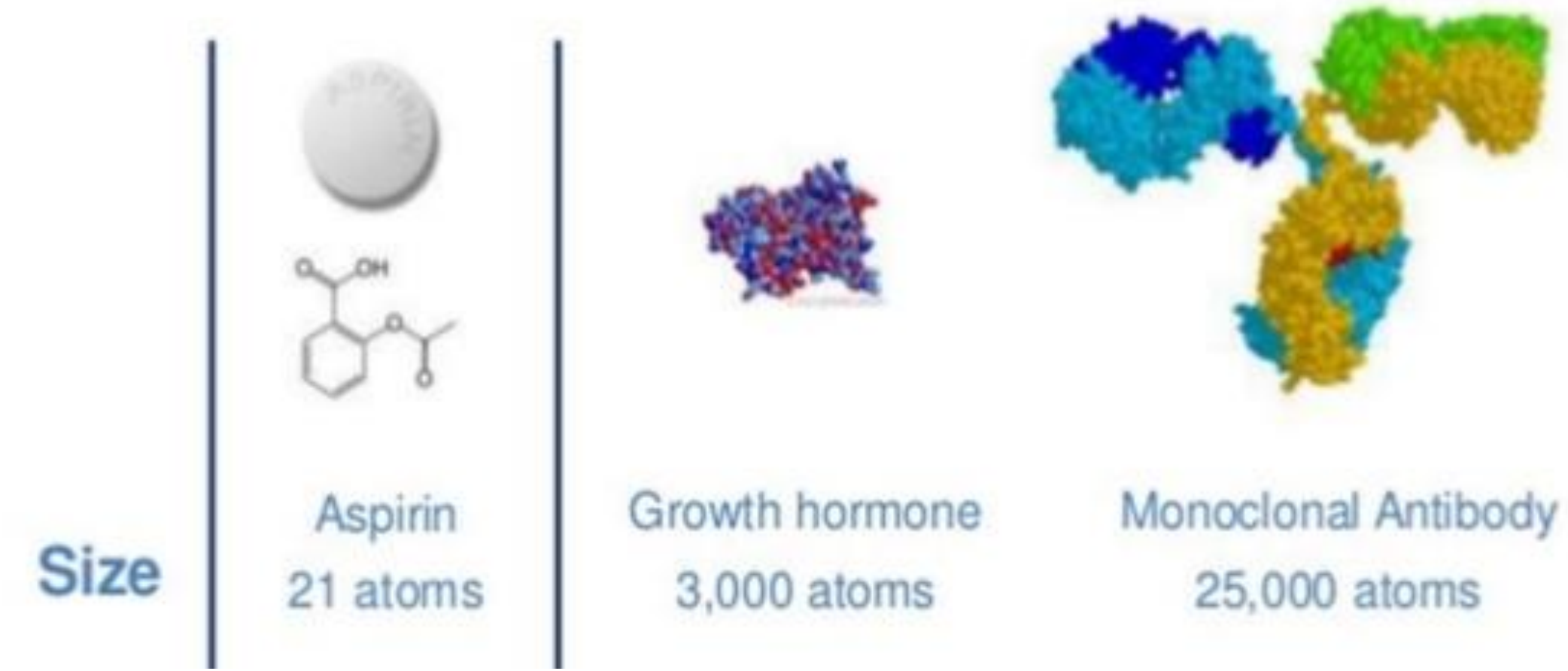
Identified a small molecule that was FDA approved in 2021

Acquired by BMS in late 2020

Our long term goal was to:

Develop small molecule therapeutics that can treat inherited cardiomyopathies

Sizes and types of drugs vary widely



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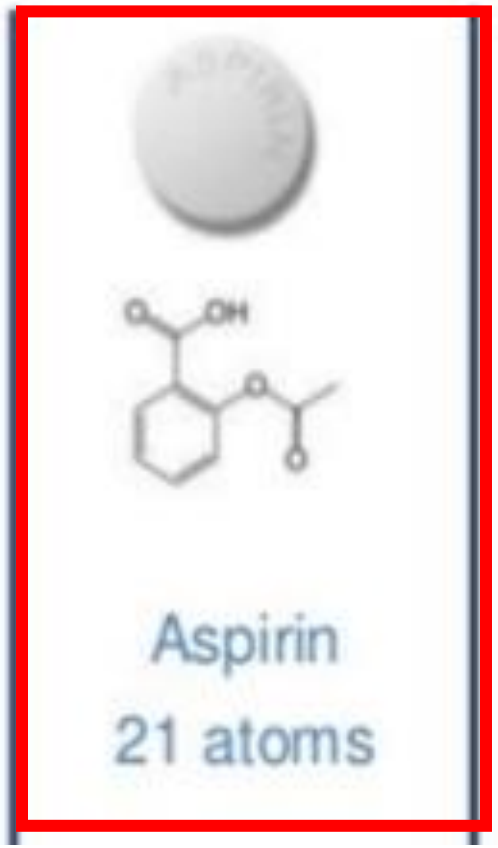


Small molecule

Are myosin modulators feasible, and if so, can they treat myosin diseases?

Approach: Find a small molecule that inhibits the myosin motor to treat HCM

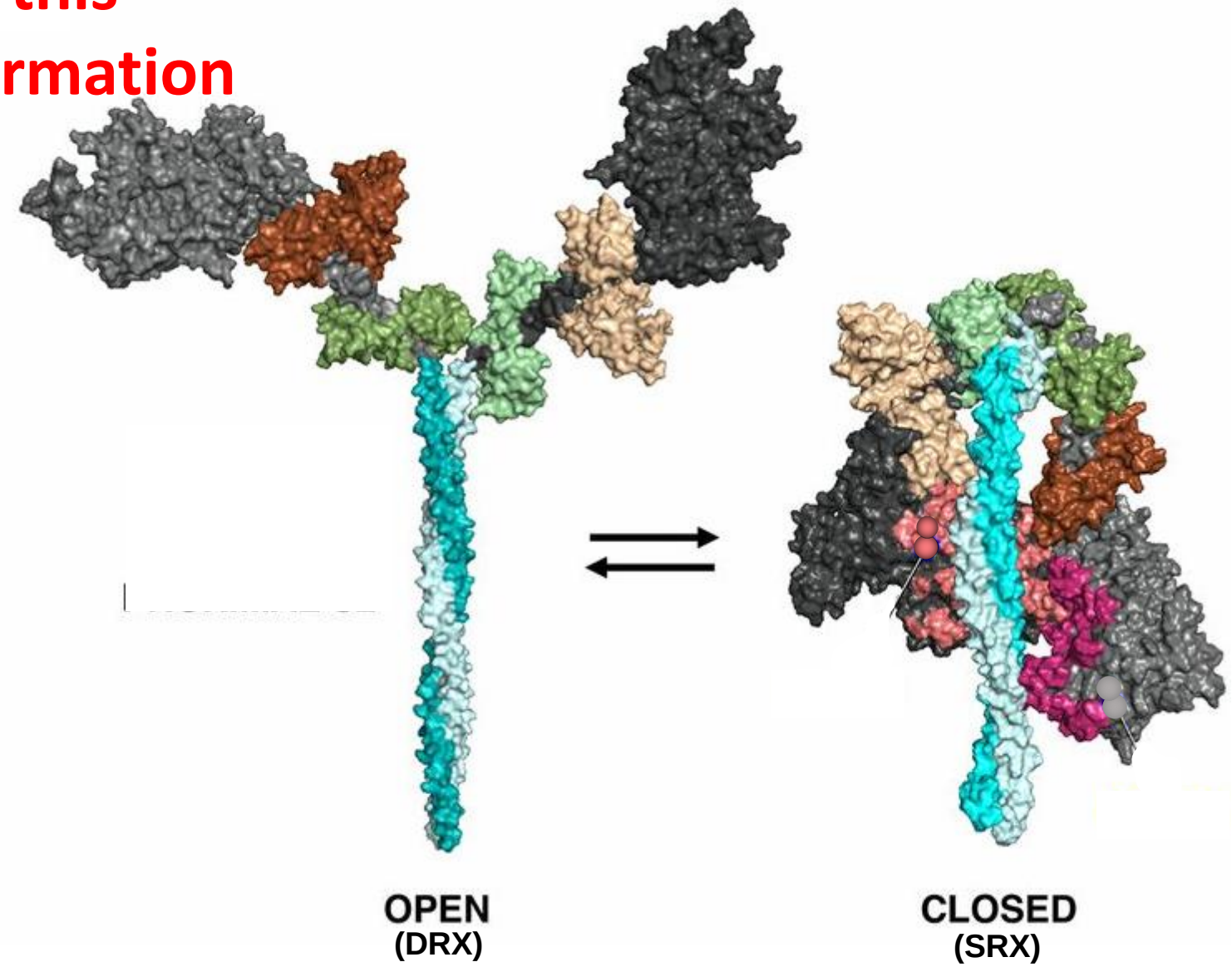
Putting the brake on the myosin motor

What is the rationale for *inhibiting* the myosin motor in HCM patients?

- **Patients with HCM have hypercontractile hearts**

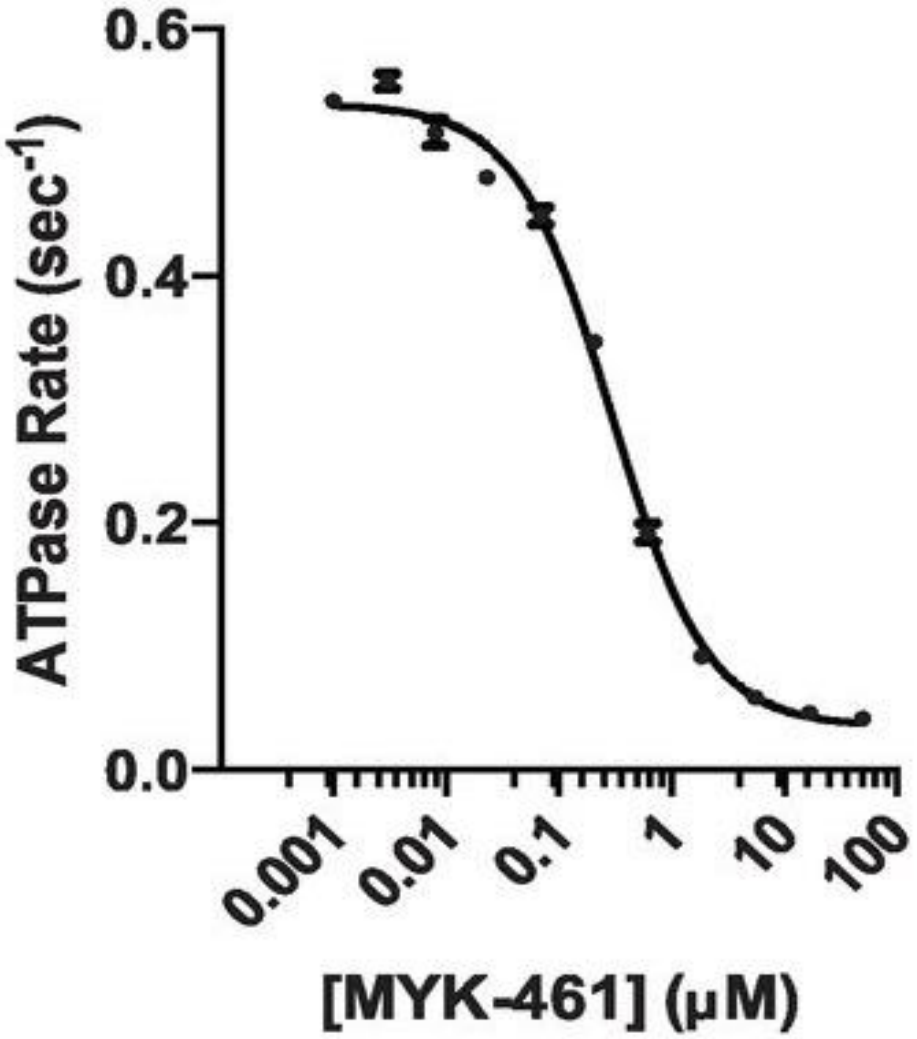
- **Many myosin mutations have increased function which can be just as bad as decreased function**

HCM mutant myosin has more of this active conformation



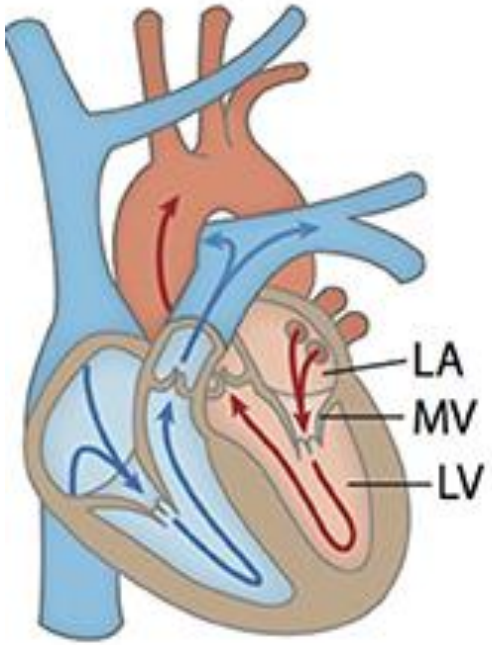
Robert L. Anderson et al. PNAS 2018;115:35:E8143-E8152

MyoKardia developed a myosin inhibitor to treat HCM patients

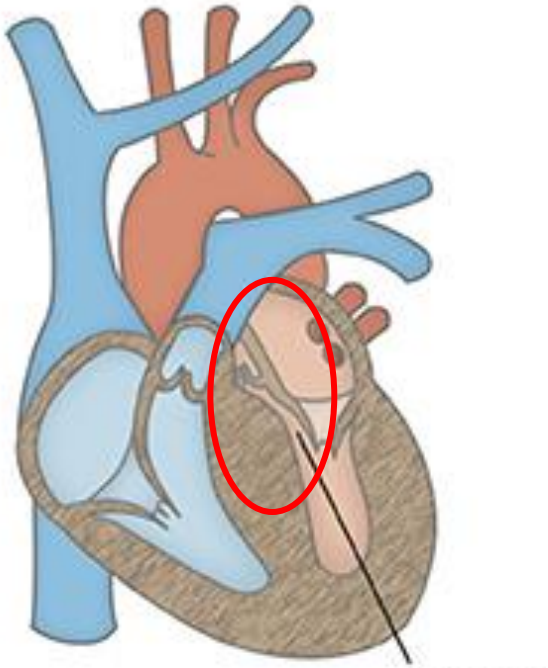


Successful clinical trials on HCM patients:

FDA approval 2021!



Normal



HCM

To extend our approach to other genes and diseases caused by mutations in the muscle contractile machinery……

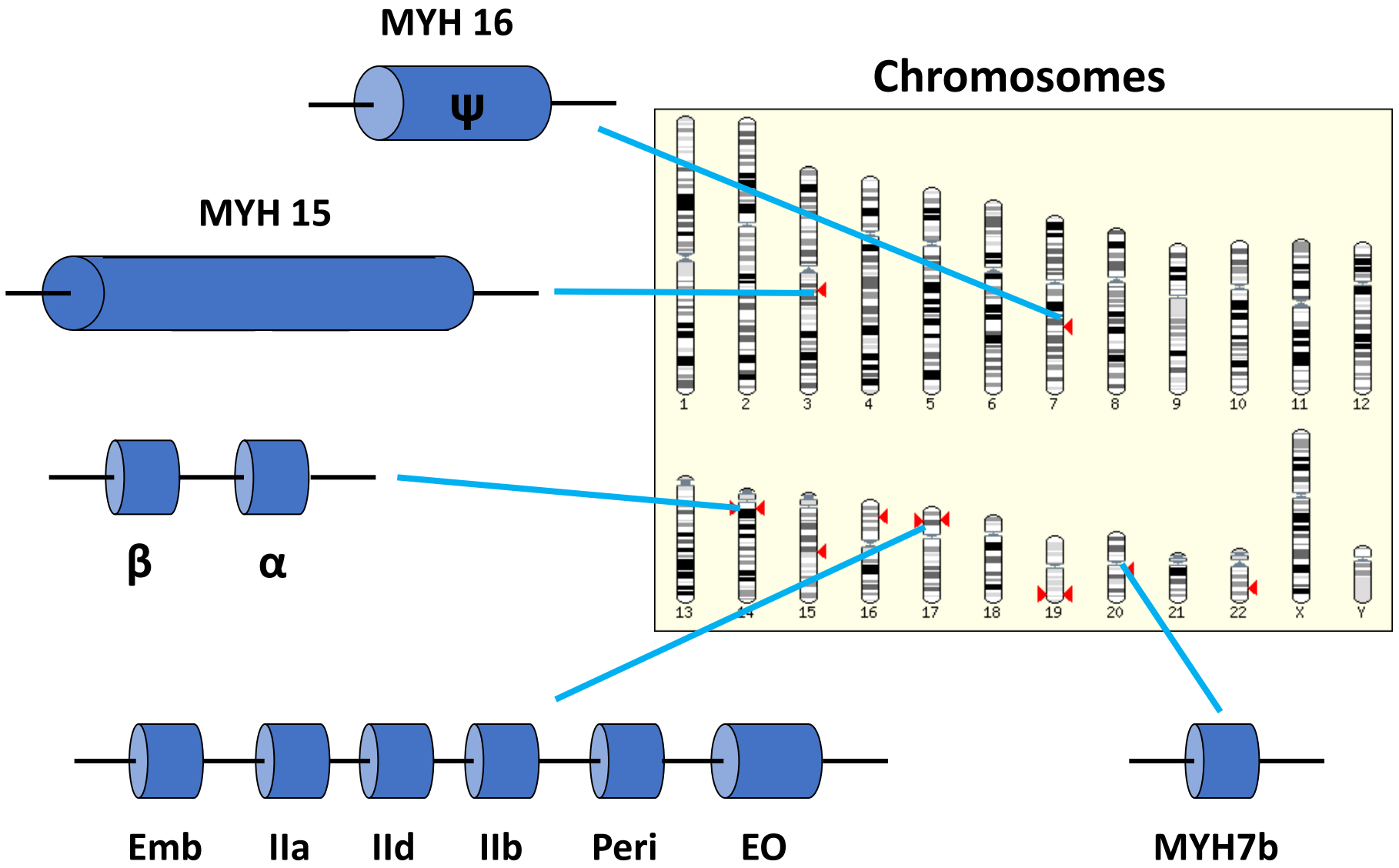
MyoKardia established the Sarcomeric Human Cardiomyopathy Registry

A registry of 7000 HCM patients and 2400 Dilated Cardiomyopathy patients in 12 Centers around the world. Clinical and DNA databases.

Will this approach work for other diseases?

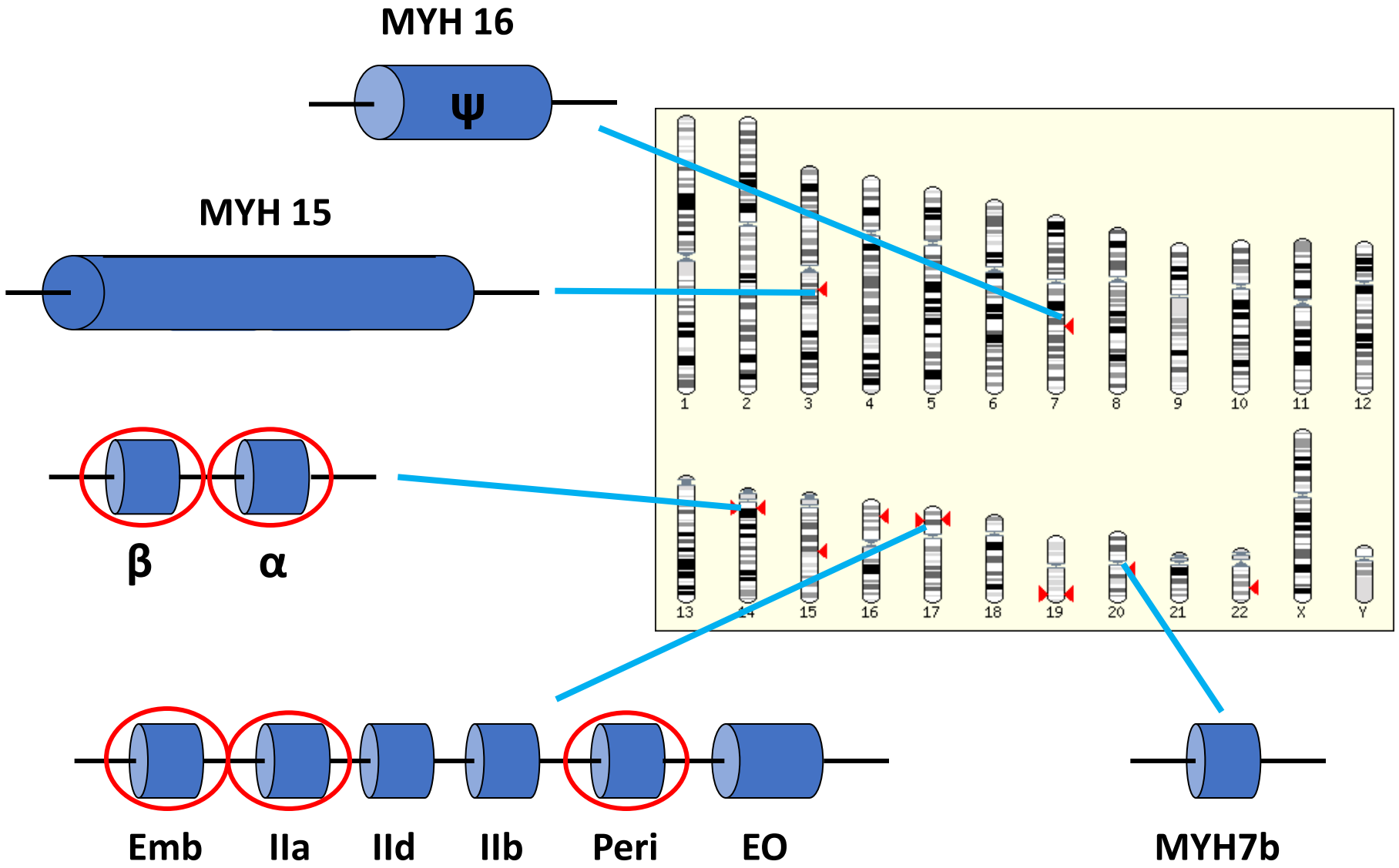
And might that include very rare diseases for which drug development might not be a viable business option?

There are many types of myosin motors in the human genome



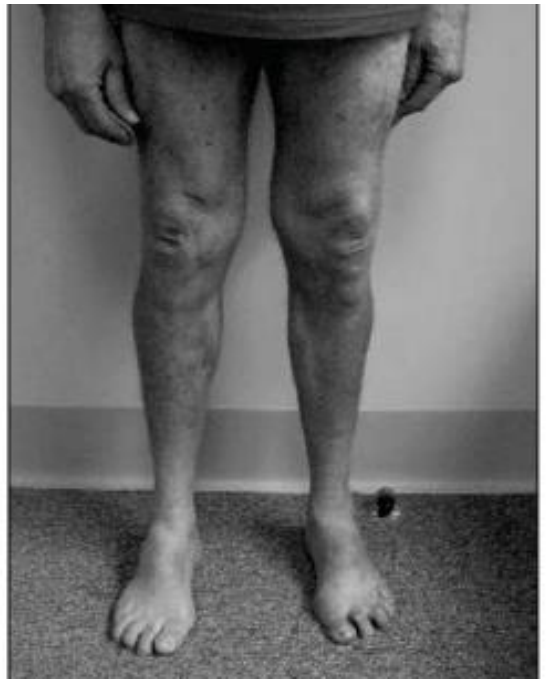
There are many “flavors” of myosin motors:

Mutations in a number of myosin genes cause a variety of muscle diseases

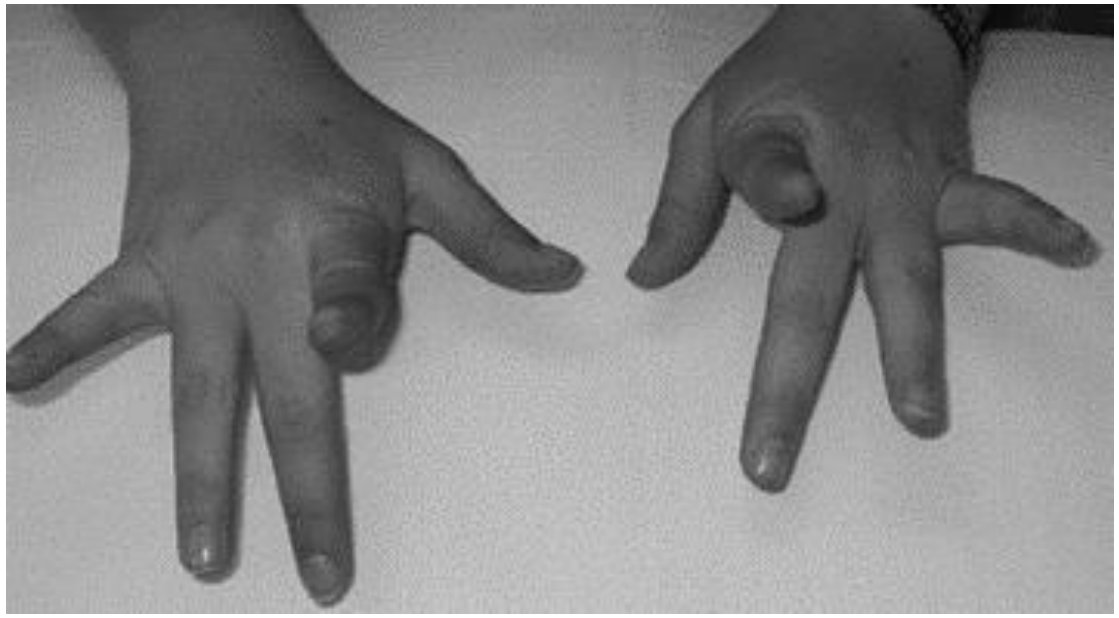


Rare diseases that might be treated with myosin modulators

Laing Distal Myopathy (MPD1): also caused by myosin mutations



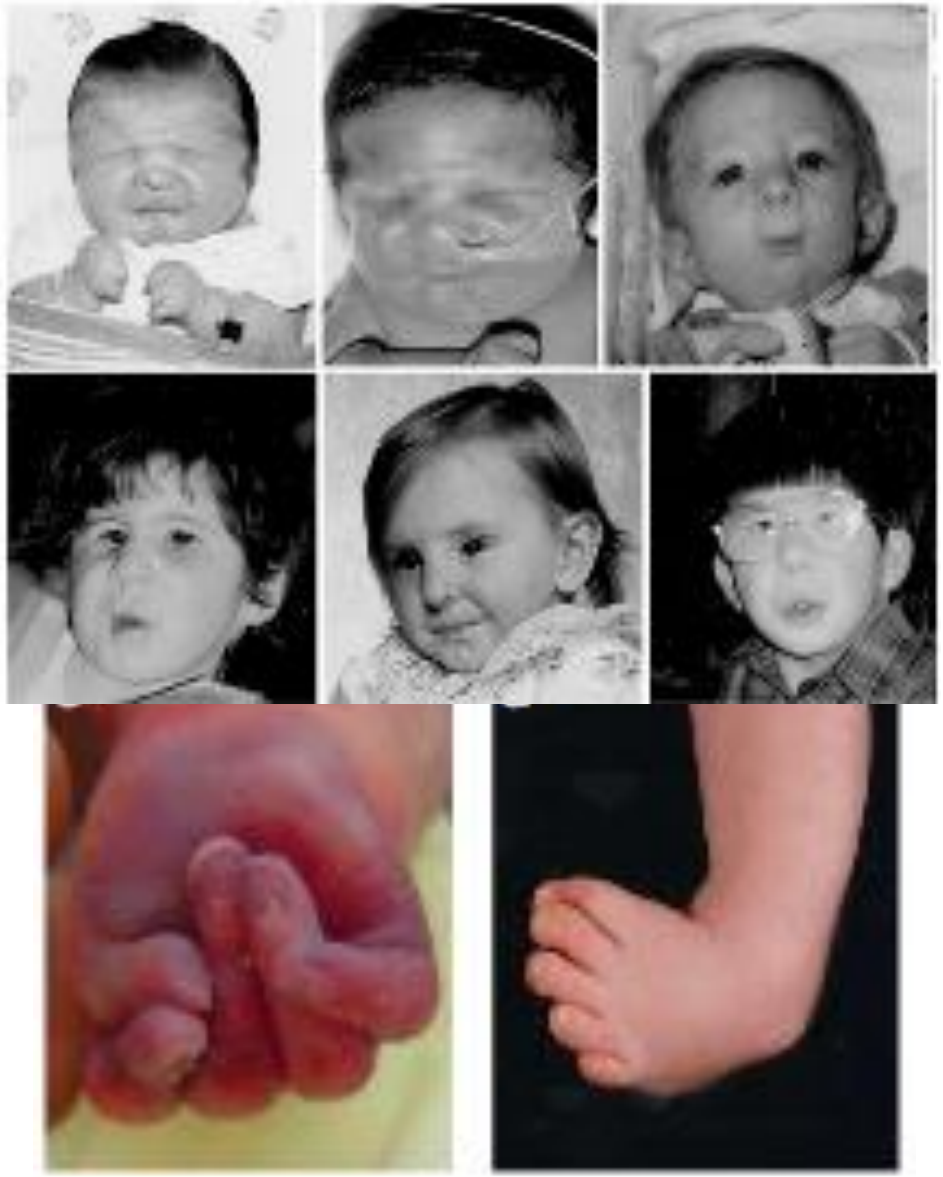
Wasting of muscles below the knees

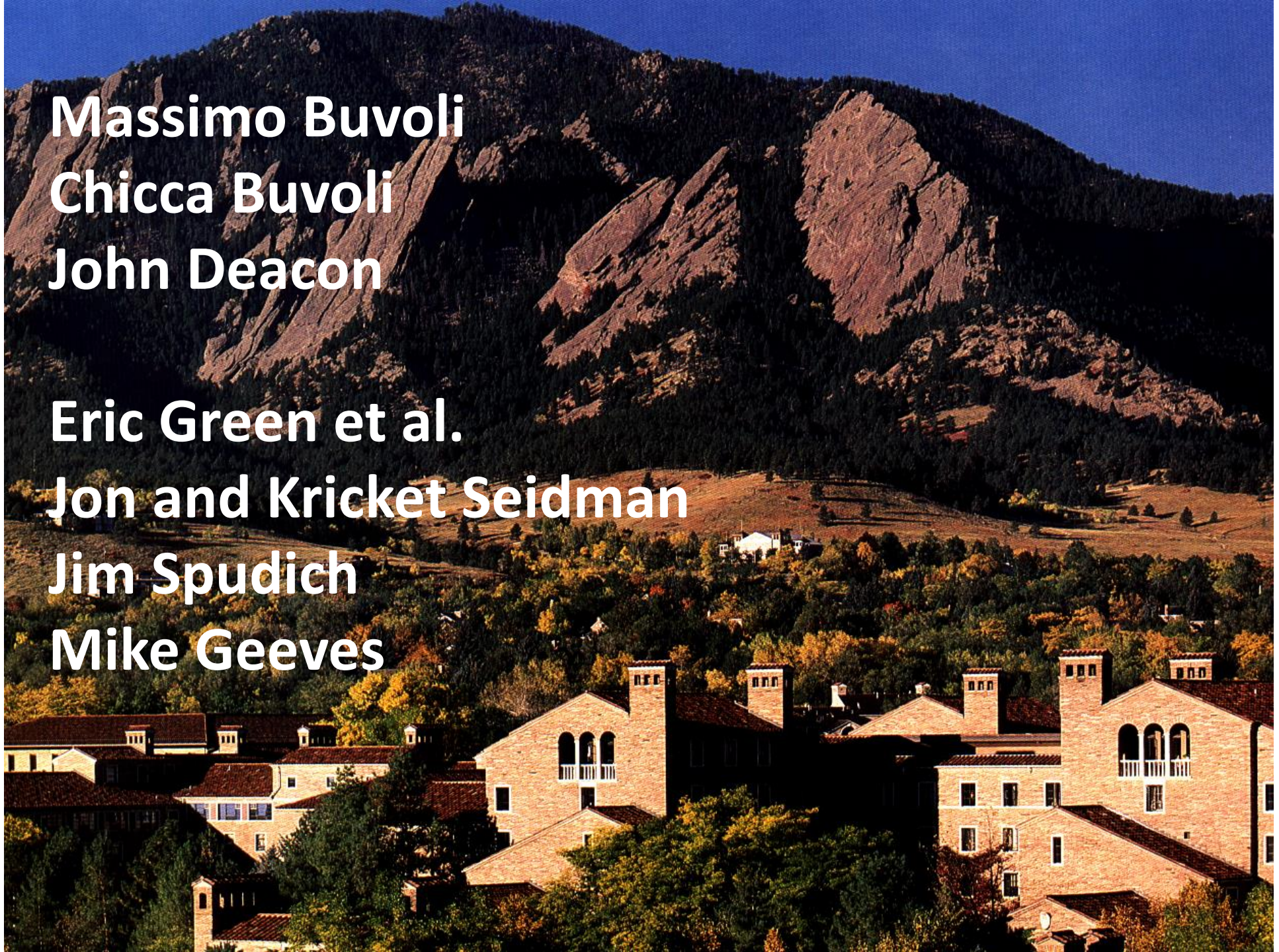


Marked weakness of third and fourth finger extension.

Freeman-Sheldon syndrome
(mutations in embryonic myosin)

Facial deformities
Joint contractures
Club feet




Massimo Buvoli
Chicca Buvoli
John Deacon
Eric Green et al.
Jon and Kricket Seidman
Jim Spudich
Mike Geeves

Many companies are trying to develop precision medicine pr personalized medicine based on genetics.

Don’t forget about biological sex!

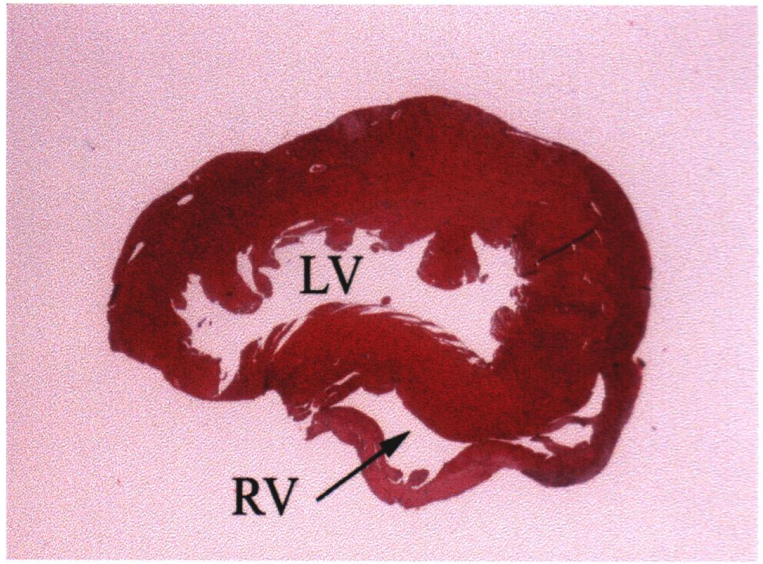
HCM has dramatic sex differences up to about age 60.

Males have much disease than females.

Most people assumed it was protective effects of estrogen.

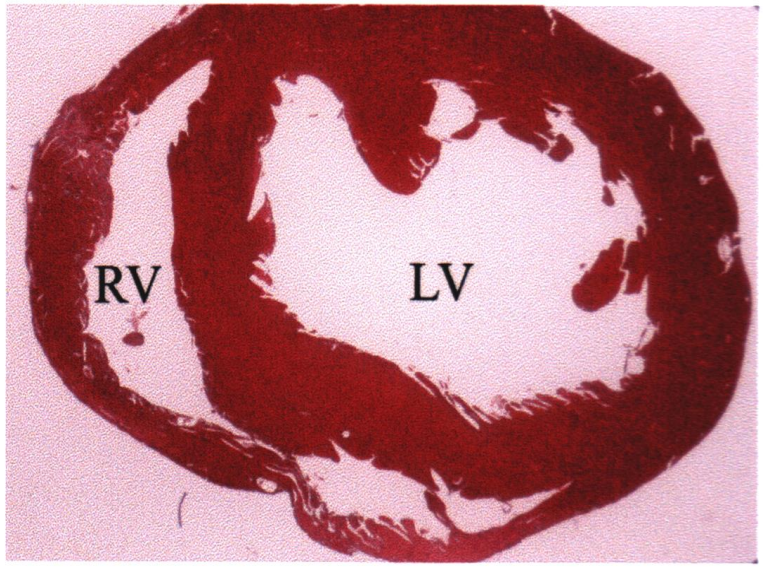
Sex differences in HCM mice

Female



Not very much disease

Male



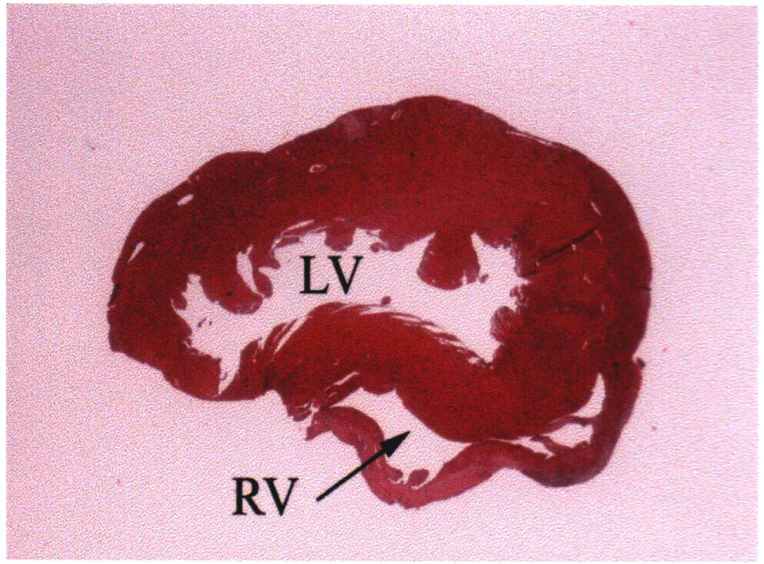
Bad

Will giving estrogen to males prevent serious HCM disease?

Will removing estrogen from females make the HCM worse?

Sex differences in HCM are not due to Estrogen

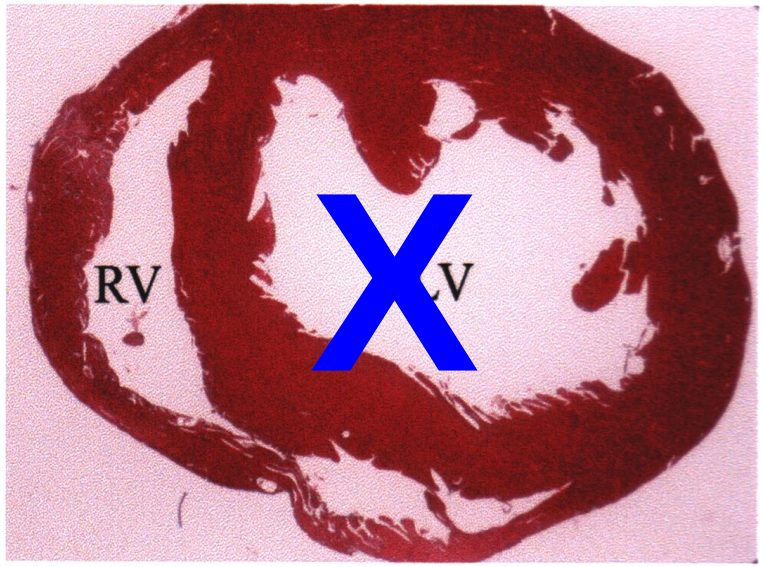
Female



- estrogen

Females did not get worse

Male



+ estrogen

All males died