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

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Genetic heart disease

As opposed to lifestyle
Genetic heart disease

hypertrophic cardiomyopathy
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
This is a beautiful single cardiac muscle cell.
There is a molecular motor called myosin that drives muscle contraction
A myosin gene mutation was identified that causes HCM in 1990

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

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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

| Size       | Aspirin 21 atoms | Growth hormone 3,000 atoms | Monoclonal Antibody 25,000 atoms |
Sizes and types of drugs vary widely

- **Aspirin**: Small molecule, 21 atoms
- **Growth hormone**: 3,000 atoms
- **Monoclonal Antibody**: 25,000 atoms

**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
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
MyoKardia developed a myosin inhibitor to treat HCM patients
Successful clinical trials on HCM patients:

FDA approval 2021!
To extend our approach to other genes and diseases caused by mutations in the muscle contractile machinery........
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
Many companies are trying to develop precision medicine or 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