GENOMIC-GUIDED THERAPIES:
CAN WE CURE CARDIOMYOPATHY?

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HEART FAILURE UPDATE 2018—TORONTO
MAY 12, 2018
DISCLOSURES

- Research support from MyoKardia, Inc to fund a patient registry
Curing Genetic Cardiomyopathy:
What Do We Need to Learn?

• How do gene mutations lead to disease?
  ○ Phenotypic spectrum and disease mechanisms
• Why do some patients do poorly and others do well?
• How can disease progression and emergence be prevented?
**GENES ➔ PATHOGENESIS ➔ TREATMENT**

Genes

Pathogenesis

Treatment

Early/Preclinical HCM
G+/LVH-

Fertilization

Birth

Adolescence+

Identify Early Phenotypes: Isolate changes caused by the mutation from changes related to disease itself

How Do Sarcomere Mutations Lead to HCM?

How can disease progression be interrupted?

Gene mutation introduced

Detectable LVH ➔ Clinical Diagnosis of HCM
**How Do Sarcomere Mutations Cause HCM? How Can Disease Progression Be Interrupted?**

1. **Sarcomere Mutation**
   - Increased Force
   - MYK-461

2. **Abnormal Calcium**
   - ATP hydrolysis
   - S

3. **Fibrosis**
   - Non-myocyte proliferation and matrix expansion
   - Activate Fibroblasts

4. **Activate TGF-beta**

Teekakirikul P et al. JCB 2012;199:417-421
MYK-461 (Mavacamten): Reduces ATPase and Force

- MYK-461 reduces ATPase rate in myofibrils and cardiomyocytes.
- ATPase rate decreases with increasing [MYK-461] concentration.
- MYK-461 affects ATP binding, ADP release, and actin binding.

Green et al, Science 2016
Early MYK461-Treatment Attenuates Hypertrophy and Fibrosis

Green et al, Science 2016
**PIioneer-HCM (Phase 2 Study): Mavacamten (MYK-461)**

**Reduces LVOT Gradients & Improves Functional Capacity**

Clinical Trials
- **EXPLORER**: pivotal study for obstructive HCM
- **MAVERCIK**: non-obstructive HCM
EARLY TREATMENT WITH DILTIAZEM: ATTENUATES LVH AND FIBROSIS (IN MICE)

• Treatment was most beneficial when started before LVH develops
  • Unable to reverse/rescue established disease
• Clinical Implications: Early pharmacologic intervention to improve Ca\textsuperscript{2+} balance may improve the natural history of HCM

PILOT TRIAL OF DISEASE MODIFICATION: DILTIAZEM VS PLACEBO IN PRECLINICAL (G+/LVH-) HCM

Pilot study: Safety and Feasibility
- Can medications be safely and reliably given to young, otherwise healthy and asymptomatic individuals?
- Can treatment response be detected?
Diltiazem Treatment: Improvement of LV Cavity Size Towards Normal

Population Mean

Wall Stress ~ $P\frac{\text{Thickness}}{\text{Diameter}}$

Lower diastolic pressures needed to fill LV
→ Geometric effects influence diastolic filling

Decrease in Thickness:Diameter Ratio

Ho, et al. JACC:Heart Failure 2015
**Genotype May Matter:**

**More Prominent Treatment Benefit for MYBPC3 Mutations**

Similar beneficial patterns seen with: CMR LV mass, serum troponin, E/E’ (p<0.01)

Response to disease-modifying treatment may vary based on genetic background
Disease Modification via Inhibition of TGF-β: Attenuate LVH and Fibrosis

Teekakirikul P, et al. JCI; 2010
Primary Endpoint: Change in LV mass

Mean difference 1 g/m² (95% CL, -3 to 6 g/m²)

p=0.60

- N=133 patients
- Randomized 1:1 to losartan 100 mg daily (n=64), or placebo (69) for 12 months

Conclusions and Future Perspectives

• No significant effect of losartan on LV mass or secondary endpoints in patients with overt HCM
  – Average age 52 years; 33% NYHA II/III

• The observed safety suggests that losartan may be used for other indications in patients with obstructive physiology

• Future studies needed to determine if ARBs can attenuate disease progression in preclinical or earlier stages of HCM
  – Right Patient?:
    • Younger- shorter disease duration, milder/reversible manifestations
    • Sarcomere mutation carriers
  – Right Outcomes?:
    • More dynamic/ responsive phenotypes

HCM♥Net
Multicenter Clinical Network

Phase II Randomized, Placebo-controlled, Double-Blind Clinical Trial of Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM

**1° Analysis Cohort**
8-30 years old, NYHA I-II, no obstruction

**Exploratory Cohort**
G+/LVH-Age 10-25 years

**Baseline**
- History
- Family History
- Genotype
- PE
- ECG
- Echo
- Biomarkers
- CMR
- CPET

**Active Run In**
- Titration over 2 week intervals to Goal Dose: Adults: 320 mg/d
- Children ≥35 kg: 160 mg/d
- Children <35 kg: 80 mg/d

**STRATIFY**
- Pre-pubertal or Post-pubertal*
- NYHA Class I or Class II
- LVWT < or ≥ 14 mm
- Group 1 or Group 2

**Randomize**
- Valsartan n ~75
- Group 1
- Placebo n ~75
- Group 1

**Evaluation at 12 and 24 months**
- History
- PE
- ECG
- Echo
- Biomarkers
- CPET and CMR at 24M

**1° Composite Outcome**
Z-score of change from baseline across domains:
- Myocardial injury
- Hemodynamic stress
- Collagen metabolism
- Functional capacity
- Myocardial fibrosis
- Cardiac morphology
- Cardiac function

**2° Endpoints**
- Safety
- Clinical outcomes
- Individual components of primary composite outcome
- Quality of Life and Physical Activity
- Alternative assessments of cardiac function
- Interactions with age, genotype, baseline characteristics

Randomization Completed May 2017 (n=178 Primary Analysis Cohort)
Follow-up To Be Completed May 2019

ClinicalTrials.gov Identifier NCT01912534
**LMNA Cardiomyopathy**

- *LMNA* encodes Lamin A/C which provides structural integrity for the nucleus and plays a role in mechano-transduction and gene expression.
- Highly penetrant.
- Heart block and atrial fibrillation are nearly universal and often present before overt CMP.
- Increased risk for cardiac arrest, heart failure and stroke.
- Gene-specific diagnosis can help guide management.
- Targeted therapies are being studied.

From Neal Lakdawala, MD, BWH
**NOVEL THERAPY FOR LMNA HEART DISEASE**

- Activation of the p38 MAPK pathway has been established in murine models of LMNA heart disease (e.g. *LMNA*<sup>H222P</sup>)
- Small molecule inhibitors of p38 MAPK have favorably influenced natural history in *LMNA*<sup>H222P</sup> mice (ARRY-371797)

16 week old LMNA<sup>H222P/H222P</sup> mice randomized to 4 weeks of placebo or p38 MAPK inhibitor (ARRY-371797)

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Choi Sci Trans Med 2012
Wu Bioorg Med Chem 2017
**NOVEL THERAPY FOR LMNA HEART DISEASE**

- Phase 2 trial of ARRY-797 in patients with heart failure caused by LMNA mutations showed:
  - Improved 6MWT
  - Decreased NT-BNP
  - Stable LVEF
- A phase 3 clinical trial of is pending

**Improved functional status in patients with LMNA HF treated with ARRY-797**

MacRae CA. Judge DP. Eur Heart J 2016:37;AS 1011
**Silencing and Editing HCM Gene Mutations**

- Injecting a short fragment of RNA (RNAi) interferes with expression of mutation
  - Expression $\downarrow \sim 30\%$
- Prevented development of HCM in mice
- Genome editing with CRISPR-Cas9
- Germline “correction” of heterozygous *MYBPC3* mutation in zygotes

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Summary

• Collaborative basic discovery and clinical translational studies can improve understanding of the molecular basis of genetic cardiomyopathies

• Mechanistic insights can begin to transform management:
  • Develop rational, mechanism-based therapy
  • Identify and target the highest risk cohorts before irreversible changes occur
Human Translational Studies
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