Acute Effects of a Small-Molecule Direct Myosin-Modulator (MYK-581) in a Mini-Pig Genetic Model of Non-Obstructed Hypertrophic Cardiomyopathy:

*In Vivo* Evidence for Contractile Regulation with Improved Compliance and Functional Reserve

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Background: Hypertrophic Cardiomyopathy (HCM)

• Hypertrophic cardiomyopathy (HCM) is a heritable cardiac disease characterized by *hyper-contraction* as well as *impaired ventricular relaxation and compliance*.
  - Hindered exercise capacity and cardiac reserve
  - Sarcomere disease (mutations)
**Background:** HCM Mini-Pig Model

✔ MYH7 R403Q mutation in Yucatan background
**Background:** HCM Mini-Pig Model

✓ MYH7 R403Q mutation in Yucatan background

![Graph showing pCa vs Tension and pCa50 values for WT and R403Q samples at 3 months and pCa 6.4.](image)

**Figure:**
- Tension (mN/mm²) graph with pCa values for WT and R403Q samples at 3 months.
- pCa50 values for WT and R403Q samples at pCa 6.4.
- EF (%) and Disarray Score graph showing differences between WT and R403Q samples.

**Background:** MYK-581 (mavacamten analog)

**Myosin-modulation** with MYK-581 could limit residual cross-bridges during diastole, improving **LV compliance and relaxation** in the mini-pig HCM model.

**What is mavacamten?**

A novel clinical-stage small molecule that regulates contractility by **DIRECT** modulation of cardiac myosin / biomechanical cycle (reduces ATPase activity)

- Inhibits the rate of phosphate release of β-cardiac myosin-S1 (preserves ADP release)
- Decreases the number of actin-binding heads transitioning from the weakly to the strongly bound state
  

- Stabilizes thick-filament, in particular, the super relaxed state (SRX) of myosin
  

- Improves compliance/distensibility
  
METHODS

- Bred male wild-type (WT) and MYH7 R403Q mutants (R403Q) littermates at 3M of age
- CV profile before/after treatment

\[ \text{β-AR reserve (DOB, 10 µg/kg/min IV)} \]
  - MYK-581 at 0.25 mg/kg IV (30min)
  - WT (n = 7, 4.2 ± 0.2 M, 18.6 ± 2.4 kg)
  - R403Q (n = 11, 4.2 ± 0.2 M, 17.8 ± 1.7 kg)
METHODS

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**ANES (ISO)**
- β-AR reserve (DOB, 10 µg/kg/min IV)
  - MYK-581 at 0.25 mg/kg IV (30min)
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**TELE**
- Chronic/Conscious LVP (telemetry)
  - MYK-581 at 1 mg/kg PO (capsule)
  - β-AR blocker (metoprolol, 2 mg/kg PO)
  - WT (n = 3) and R403Q (n = 4)
RESULTS: Altered Cardiac Function in MYH7 R403Q Mutants

- **Hyper-contractile**

...but unchanged $dP/dt_{\text{max}}$ (velocity)
RESULTS: Altered Cardiac Function in MYH7 R403Q Mutants

- Hyper-contractile
  - ...but unchanged dP/dt_max (velocity)
- Diastolic Impairment
  - Decreased compliance
RESULTS: Altered Cardiac Function in MYH7 R403Q Mutants

- **Hyper-contractile**
  - but unchanged $dP/dt_{max}$ (velocity)

- **Diastolic Impairment**
  - Decreased compliance and
  - Hindered relaxation

**Graphical Representation:**
- **LVP (mmHg) vs. LVV (mL)**
  - WT vs. R403Q
  - $E_{es}$ increased
  - $\tau$ increased
  - $EDP$ increased
  - $dP/dt_{min}$ (velocity) unchanged
RESULTS: Altered Cardiac Function in MYH7 R403Q Mutants

- Hyper- contractile
  …but unchanged dP/dt max (velocity)
- Diastolic Impairment
- Decreased β-AR cardiac reserve
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

- Reduced Hyper-contractility

![Graph showing normalized cardiac function comparison between R403Q and WT with MYK-581 treatment.](image-url)
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

- Reduced Hyper-contractility

- ...but preserved/improved stroke volume/work
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

- Reduced Hyper-contractility (w/ preserved SV)
- Improved Diastole (Compliance)

...increased EDV with decreased EDP
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

- Reduced Hyper-contractility (w/ preserved SV)
- Improved Diastole (Compliance)

...increased EDV with decreased EDP
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

✓ Reduced Hyper-contractility (w/ preserved SV)

✓ Improved Diastole (Relaxation)

shortened tau and lowered EDP (vs. METO)
RESULTS: MYK-581 Normalized Cardiac Function in MYH7 R403Q

- Reduced Hyper-contractility (w/ preserved SV)
- Improved Diastole (Compliance/Relaxation)
- Restored β-AR cardiac reserve
CONCLUSIONS

Direct myosin modulation with MYK-581 (a mavacamten surrogate) in genetic HCM normalized systolic function, while improving ventricular compliance in vivo

• Results support the potential for mavacamten to:
  - Normalize inotropy
  - Improve diastolic function

Potential therapeutic advantage over beta-blockers
Mechanistic support for the salutary observations in HCM
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