**Aficamten, a Selective Small-Molecule Cardiac Myosin Inhibitor for the Potential Treatment of Hypertrophic Cardiomyopathy**


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**ABSTRACT**

Hypertrophied cardiomyocytes increase their contractility and sarcomere length to accommodate the increased load and pressure, causing hypertrophic cardiomyopathy (HCM). Strikingly targeting this sarcomere repurposing mechanism promises to alleviate cardiac symptoms in patients with hypertrophic HCM, as demonstrated by the first-in-class cardiac myosin inhibitor, aficamten. Here, we describe the next-in-class small molecule inhibitor of cardiac myosin, aficamten (-)blebbistatin. Aficamten inhibits the myosin ATPase activity and calcium transients and reduces fractional shortening and contraction velocity in adult rat ventricular cardiomyocytes isolated and loaded with the strongly actin-bound force-generating state. In single cardiomyocytes containing cardiac sarcomeres, in HCM.

**METHODS**

**Preparation of Reagents**

Aficamten was prepared in a 100% ethanol/DMSO solution at concentration of 10 mg/ml. DMSO was prepared at 1% in 95% ethanol. Compounds were kept at -80°C in a freezer until used. Aficamten stock solutions were prepared by diluting the 10 mg/ml stock in 1% DMSO.

**ATPase Assay**

Aficamten and vehicle were metabolically labeled with [3-3H]ATP and myosin subfragment-1 or bovine cardiac HMM was prepared as described in Hwee et al. (2015).

**RESULTS**

Aficamten selectively inhibits the ATPase activity of cardiac and slow skeletal cardiomyocytes and in vitro. Aficamten is a small molecule that selectively inhibits cardiac myosin ATPase activity and contractility in vitro.

**SUMMARY**

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