Hypertrophic cardiomyopathy (HCM) is a prevalent heritable cardiac disorder, characterised by unexplained left ventricular hypertrophy (LVH) with the triad of myocyte hypertrophy, disarray, and interstitial fibrosis. Such pathological hallmarks impact diastolic function and contribute to adverse clinical outcomes: arrhythmias, progressive heart failure and sudden cardiac death. To date, none of the available armamentaria has been shown to fundamentally modify disease progression, or to benefit genotype-positive, phenotype-negative or preclinical HCM patients. Multiple genetic studies have identified considerable numbers of HCM-causing mutations in human sarcomere protein genes, and mice engineered to carry such human mutations recapitulated key phenotypes of HCM. This has provided remarkable opportunities to identify the novel therapeutics at the molecular levels, and allowed us to integrate gene-based diagnostics into clinical management of preclinical HCM. Studies in HCM mouse models have illustrated the importance of activated transforming growth factor beta (TGF-β) pathway in the early development of HCM. Treatment with either TGF-β neutralising antibodies or with angiotensin II type 1 receptor antagonist, losartan, was shown to retard and prevent HCM development in mouse models. Lately, MYK-461, the first allosteric inhibitor of the cardiac myosin adenosine triphosphate (ATPase), has been shown to reduce left ventricular contractility and attenuate HCM development in mouse models. Clinical trials are currently underway to evaluate and investigate these two promising disease-modifying therapies in HCM patients.

REFERENCES