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HYPERTROPHIC CARDIOMYOPATHY: PATHOGENESIS, THERAPIES AND DISEASE MODULATION

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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.¹ Such pathological hallmarks impact diastolic function and contribute to adverse clinical outcomes: arrhythmias, progressive heart failure and sudden cardiac death.² 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.^{1–3} 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.² 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.⁴ 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 of HCM.⁵ Clinical trials are currently underway to evaluate and investigate these two promising disease-modifying therapies in HCM patients.

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