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MYK-491, A Novel Small-molecule Cardiac Myosin Activator Increases Cardiac Systolic Function And Preserves Mechanical Efficiency: Pre-clinical In Vivo And In Vitro Evidence

Author Block: Sarah Fernandes, Angelos Oikonomopoulos, Sarah K Jimenez-MacInnes, Myokardia, San Francisco, CA; Roozbeh Aschar-Sobbi, TARA Biosystems, New York, NY; Marcus Henze, Marius Sumandea, Fen Gan, Robert L Anderson, **Carlos L del Rio**, Myokardia, San Francisco, CA

Abstract:

Introduction: Cardiac myosin motors have been shown to efficiently convert ATP to mechanical force. MYK-491 is a novel small-molecule selective allosteric activator of cardiac acto-myosin that leverages such efficiency, increasing the number of force-producing cross-bridges while preserving their detachment dynamics. As such, *MYK-491 could increase systolic performance without affecting resting tension*. These *in vivo* and *in vitro* experiments evaluated the acute responses to MYK-491 in healthy dogs and human-derived cardiomyocytes (hiPSC-CMs). **Methods**: *In vivo*: Beagle dogs (n = 6) were chronically instrumented for arterial pressure and LV pressure-volume (LVPV) recordings. Systemic/LV hemodynamics, geometry, and load-independent function were examined before/following MYK-491 (3 mg/kg PO). *In vitro*: Functional (cellular morphology and engineered-tissue tension) as well as metabolic responses to MYK-491 (at matching concentrations) were studied in hiPSC-CMs. **Results**: In conscious dogs, MYK-491 increased ($P<0.05$) stroke-volume (+17 ± 2%) and ejection fraction (+18 ± 4%), as well as end-systolic elastance (7.1 ± 1.0 vs. 5.0 ± 1.5 mmHg/mL) and pre-load recruitable stroke-work (121 ± 6 vs. 94 ± 7 mmHg*), indicating an enhanced ability to generate work at a given load. As a result, MYK-491 increased stroke-work (SW: +15 ± 4%) while preserving the pressure-volume-area (PVA: -9 ± 5%), improving ventricular mechanical efficiency (SW/PVA). In hiPSC-CMs, MYK-491 increased ($P<0.05$) indices of systolic contraction (+34 ± 13%) and tension (+44 ± 7%), while maintaining oxygen consumption rates (-5 ± 1%, $P<0.05$). Notably, MYK-491 also preserved resting (end-diastolic) stiffness*in vivo* (Eed: 1.1 ± 0.2 vs. 1.0 ± 0.4 mmHg/mL, NS) and *in vitro* (+5 ± 4%, NS), showing mild prolongation of the contraction duration in both settings (+15 ± 2% and +13 ± 5%, respectively). **Conclusion**: Direct acto-myosin activation with MYK-491 has a unique cardiovascular profile characterized by improvements in systolic performance/work with both preserved efficiency and negligible effects in resting end-diastolic properties.