Inhibition of Lysyl Oxidase Like-2 (LOXL2) reduces cardiac interstitial fibrosis in mice

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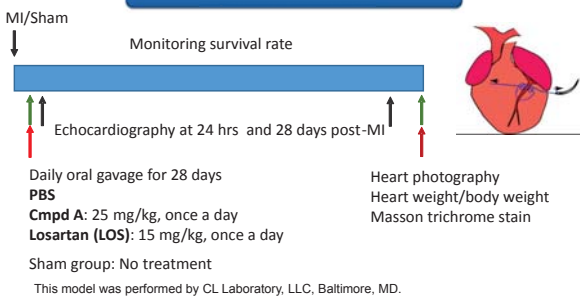
Introduction

Lysyl oxidases are a family of enzymes responsible for the conversion of the primary amine group of (hydroxyl-) lysine residues to the corresponding aldehyde. In extracellular matrix proteins, lysyl oxidases contribute to cross-linking, thereby stabilising areas of fibrosis that occur following tissue injury. Accumulation of cross-linked extracellular matrix and the resulting excessive fibrosis can ultimately progress to organ failure.

Yan et al (DOI: 10.1038/ncomms13710) have recently shown that an enzyme that crosslinks collagen—Lysyl Oxidase-Like-2 (LOXL2)—is essential for interstitial fibrosis and mechanical dysfunction of pathologically stressed hearts, with other lysyl oxidase family members less upregulated during cardiac fibrosis. Importantly, in diseased human hearts, LOXL2 is upregulated in cardiac interstitium, with levels correlating with the extent of collagen crosslinking and resultant cardiac dysfunction. LOXL2 is also elevated in the serum of heart failure (HF) patients, correlating with other HF biomarkers, suggesting a conserved LOXL2-mediated mechanism of human HF.

Pharmaxis has developed small molecule mechanism-based inhibitors that are selective for LOXL2 over ubiquitous LOX and have drug-like properties.

Experimental protocol



This model was performed by CL Laboratory, LLC, Baltimore, MD.

Functional measurements

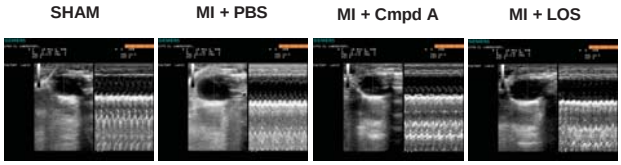


Fig. 3
Representative photos of echocardiograms 28 days post myocardial infarction

Cmpd A improves cardiac function

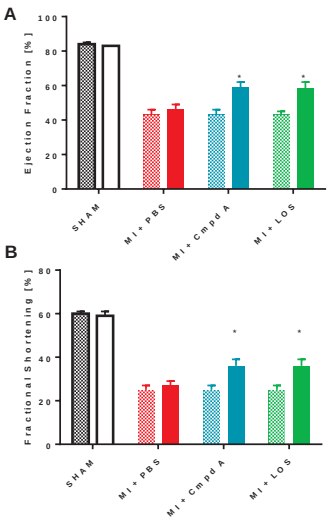


Fig. 5 A and B
Changes in cardiac function as measured by echocardiography at day 1 (hatched column) and day 28 (solid column)

Cmpd A is a selective LOXL2 inhibitor

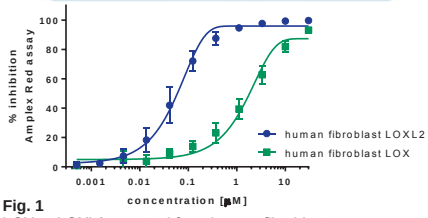


Fig. 1
LOX or LOXL2 secreted from human fibroblasts was pre-incubated with inhibitor for 30 min and activity was measured in physiological buffer solution

Myocardial infarction

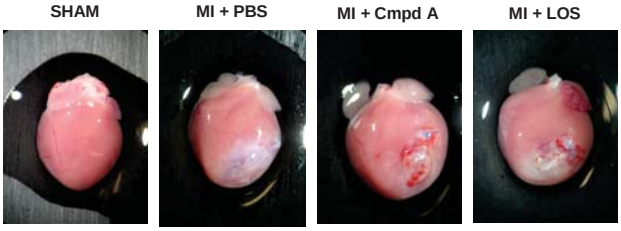


Fig. 4
Representative photos of hearts at the time of sacrifice

Cmpd A reduces area of fibrosis

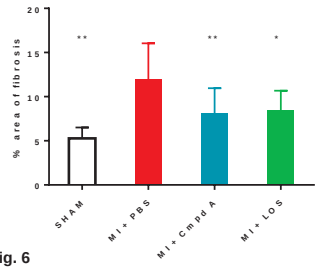


Fig. 6
Area of fibrosis measured by Mason Trichrome straining

Inhibition (IC_{50}) [nM]	
rec human LOXL2	24
rec mouse LOXL2	20
human LOXL2	40
human LOX	1800
bovine LOX	1600
rec human LOXL1	1700
rec human LOXL3	38
rec human LOXL4	100

Table 1
Pharmacology of Cmpd A against other lysyl oxidases
No inhibition (IC_{50} >30 μM) of other amine oxidases (SSAO, MAO-A and MAO-B)

Summary

Pharmaxis has developed small molecules that selectively inhibit LOXL2 with nanomolar potency
LOXL2 inhibitor

- *improve cardiac function after myocardial infarction*
- *and reduce the area of fibrosis.*

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