IMB-1018972, a novel first-in-class partial fatty acid oxidation (pFOX) inhibitor improves cardiac remodeling and function post-myocardial infarction

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BACKGROUND

Myocardial fatty acid (FA) and glucose metabolism are tightly regulated in health to meet high energy demand. Dysregulation occurs in acute ischemia (reliance on anaerobic glycolysis) while there is a marked increase in mitochondrial FA oxidation during reperfusion. In heart failure (HF) glycolysis is partially uncoupled from glucose oxidation due to reduced pyruvate dehydrogenase (PDH) activity, reducing the efficiency of energy generation. FA metabolism yields ~20% less ATP than glucose for the same O_2 consumption. Thus, inhibition of FA oxidation shifts metabolism toward glucose, increasing PDH activity and the efficiency of ATP generation. We examined the ability of IMB-1018972 (IMB-101) a novel partial FA oxidation (pFOX) inhibitor to mitigate left ventricular (LV) dysfunction and remodelling after myocardial infarction (MI).

METHODS

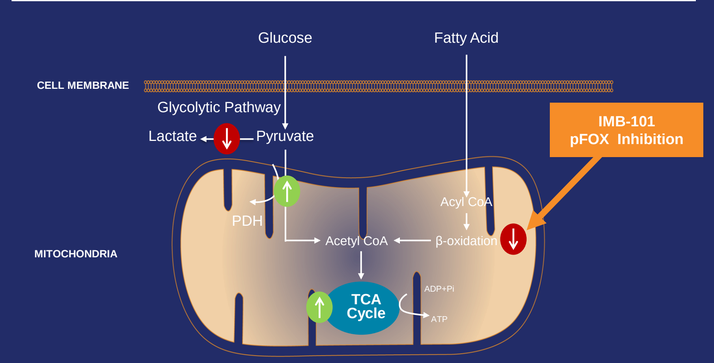
12-week old C57BL/6 male mice underwent permanent left coronary artery ligation or sham surgery. Mice received saline (CON) or IMB-101 at 10 and 30 mg/kg/d (IMB10 or 30) from day 1 (D1) post-MI, or IMB-101 30 mg/kg/d from D7 post-MI (DEL30) via osmotic mini-pump. Cardiac functions were assessed by conscious echocardiography at D1, D7 and D28 post-MI, with terminal invasive hemodynamics and cardiac fibrosis quantification (Masson's trichrome). Statistical methods used one-way ANOVA (LVEDP & fibrosis) or mixed-model two-way ANOVA (LVEF), both using post-hoc Fisher's LSD tests.

RESULTS

Echocardiography assessments showed LV ejection fraction (LVEF) was reduced in CON mice at D1 (39±2%) falling to 34±2% by D28. In contrast, IMB10 mice showed a significant increase from 34.8+2.6% (D1) to 44.4+2.6 on D7 and 53.6+4.2% on D28 ($p<0.001$). Similarly IMB30 mice showed an increase in LVEF from 38.5±3% (D1) to 48%±4% on D28 ($p<0.001$) that was also observed in DEL30 mice (42±1.8% to 48.5±4%; $p<0.01$) on D28. IMB30 mice had lower LV end-diastolic pressure (LVEDP) vs CON mice (5.3±0.7 vs 7.3±0.6 mmHg; $p<0.01$) on D28. IMB30 mice exhibited markedly less cardiac fibrosis than CON mice (6.9±0.9 vs 9.7±0.8%; $p<0.01$) with a trend to lower fibrosis for both IMB10 (7.7± 1.0%) and DEL30 mice (8.3±1.2%).

Metabolic defects in cardiomyocytes contribute to major forms of heart disease. Mitotropic agents such as IMB-101 restore mitochondrial oxidative homeostasis, reduce O_2 consumption and increase ATP generation to preserve cardiomyocyte cell health

IMB-101 is a pro-drug of three active metabolites



In MI mice **IMB-101** treatment:

- **progressively improved cardiac function from Day-1 to Day-28**
- **reduced myocardial fibrosis**
- **reduced cardiac remodeling**
- **enhanced cardiac tissue repair**

pFOX inhibition is a promising therapeutic strategy to augment mitochondrial energetics in ischemic heart tissue

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DISCUSSION & CONCLUSION

IMB-1018972 improved LV systolic function, reduced LVEDP and myocardial fibrosis and promoted cardiac tissue repair in a murine model of post-MI HF. These findings support a therapeutic strategy for pFOX inhibition with the novel cardiac mitotrope IMB-101 to augment cardiomyocyte energetics in the context of myocardial ischemia and HF.

FIGURE 1

Study design & assessments

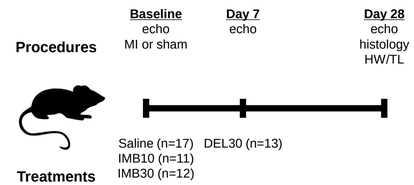


FIGURE 2

IMB-101 reduces cardiac remodeling

(heart weight to tibia length ratio)

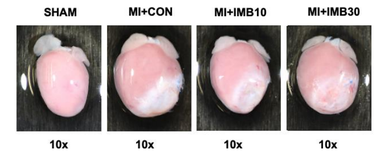


FIGURE 3

IMB-101 improves LV systolic and diastolic function post-MI

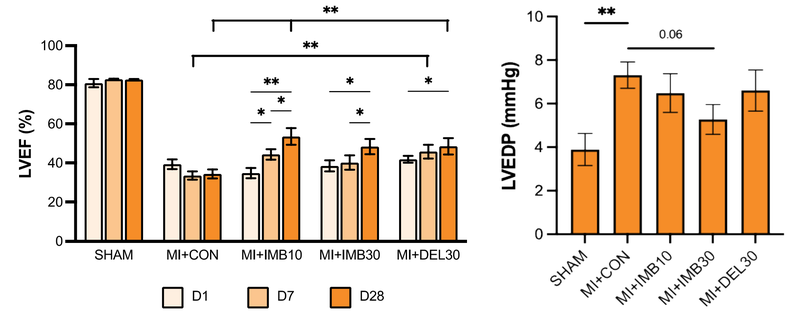
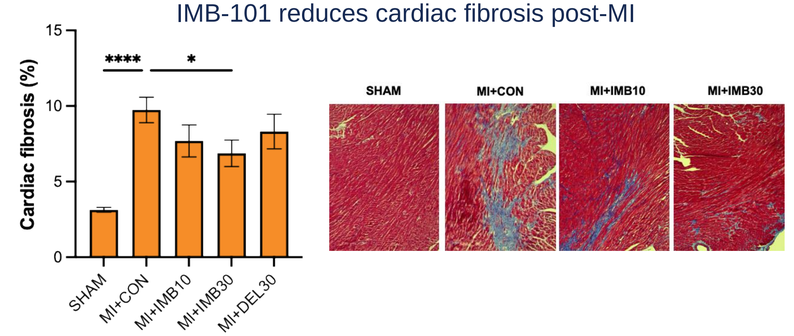


FIGURE 4

IMB-101 reduces cardiac fibrosis post-MI



DISCLOSURE INFORMATION

Author Disclosures: MH, JP & PC are employees /share holders in Imbria Pharmaceuticals, Inc; AL is a Managing Director at RA Capital Management LLC, an Imbria Pharmaceuticals, Inc investor.