

Improvement in left ventricular function due to a reduction of myocardial fibrosis following myocardial infarction using a purpose designed novel anti-fibrotic drug FT-011.

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Introduction: Myocardial fibrosis, is a hallmark feature of chronic heart failure. Following myocardial infarction (MI), reactive fibrosis distal to the infarct site, results from pathological deposition of excess collagen and has adverse effects on cardiac function. We evaluated the role of a novel antifibrotic drug FT-011 in preventing reactive fibrosis and preserving ventricular function.

Methods: In vitro, isolated neonatal cardiac fibroblasts were stimulated with angiotensin II (AII) or TGF- β , to assess whether FT-011 either alone or in combination with Irbesartan (Irb) had an effect on collagen synthesis (assessed by proline incorporation). In vivo, 10 week old Sprague Dawley rats underwent left anterior descending artery ligation to induce MI (or sham procedure) and were treated for 4 weeks with FT-011 or vehicle, starting 1 week post surgery. Left ventricular (LV) function was assessed with echocardiography (day 2 and 35) and with cardiac catheterization (day 35). Total collagen (TC) deposition (picrosirius red staining), and collagen subtypes I and III (C-I, C-III) using immunohistochemistry were assessed

Results: Cell culture experiments demonstrated a dose dependent reduction of collagen synthesis with FT-011 in response to both AII and or TGF- β stimulation ($p < 0.01$), and a further reduction of collagen synthesis with FT-011+Irb. A summary of in vivo results is reported in the table. MIs were of comparable size and treatment with FT-011 significantly reduced pathological deposition of TC (as well as C-I and C-III) in the myocardium, resulting in improved LV systolic function, normalization of diastolic function parameters and improvement in heart failure. Lung/body weight ratio was significantly reduced with FT-011 ($p < 0.05$) further supporting improvement in LV function.

Table: 35 day data [mean (SEM)].									
	FAC %	LVED Vol(ml)	LVES Vol(ml)	LVED-Diam(cm)	LVES Diameter(cm)	E:A ratio	Deceleration time (ms)	PRSW slope(mmHg)	TC (%)
Sham+Vehicle	66.40(1.52)	0.43(0.04)	0.08(0.01)	0.83(0.02)	0.46(0.03)	2.45(0.17)	34.75(1.49)	72.77(6.70)	1.03(0.08)
MI+Vehicle	27.56(1.18)**	0.90(0.08)#	0.48(0.04)**	0.99(0.03)#	0.81(0.03)**	3.46(0.52)	50.09(1.78)#	53.49(4.66)	2.23(0.24)#
MI+FT-011	42.69(2.27)**	0.53(0.04)#	0.15(0.02)**	0.92(0.03)	0.70(0.03)*	2.00(0.26)*	38.64(1.18)**	65.15(3.04)*	1.5(0.18)#

* $p < 0.05$, # $p < 0.01$, ** $p < 0.0001$ (MI+Vehicle compared to Sham+Vehicle and MI+FT-011 compared to MI+Vehicle). FAC= fractional area change, PRSW=preload recruitable stroke work. LVES=LV end systole, LVED=LV end diastole.

Conclusion: Post MI treatment with FT-011 improved heart function by reducing the pathological remodeling of collagen in the ventricle.