Triiodothyronine as a novel therapeutic approach for repair/regeneration after myocardial infarction

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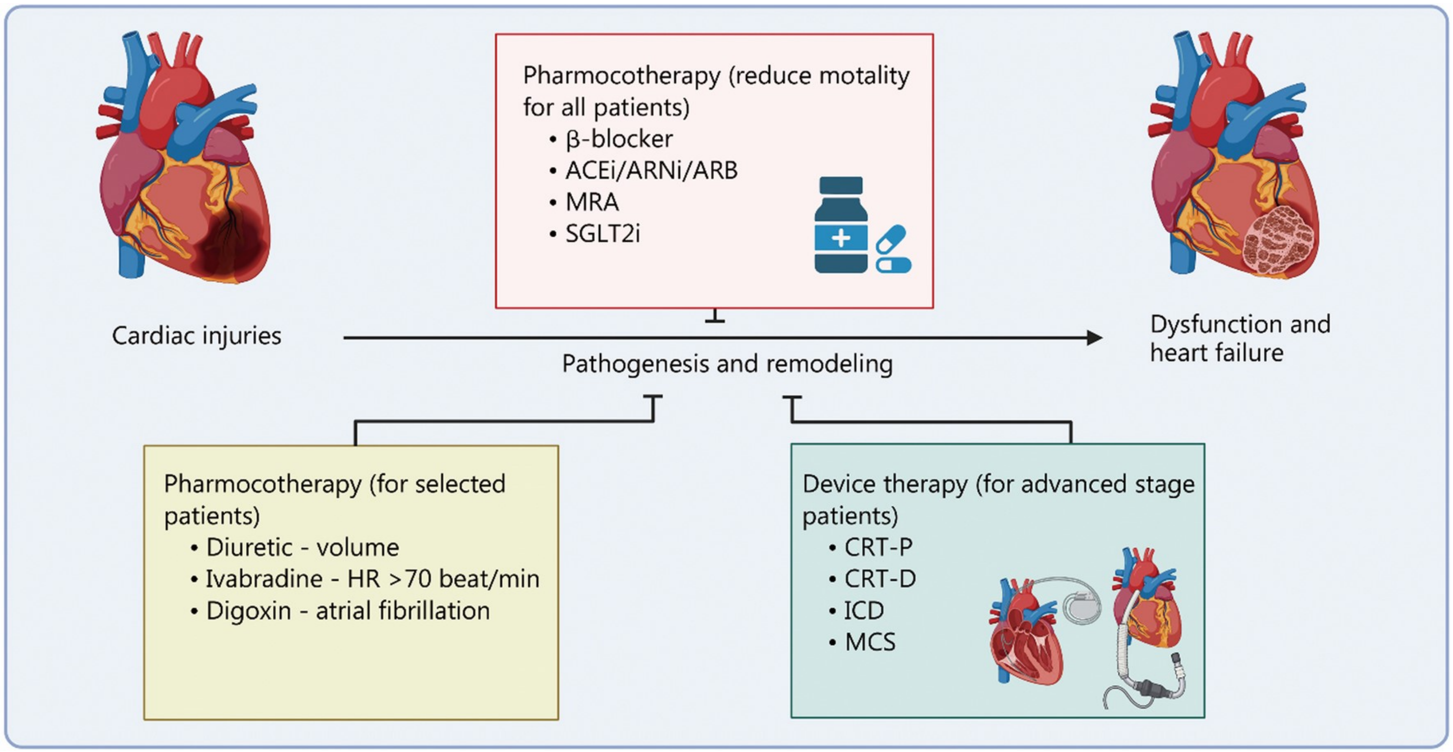
Cardiac Regeneration: The holy grail of contemporary cardiology

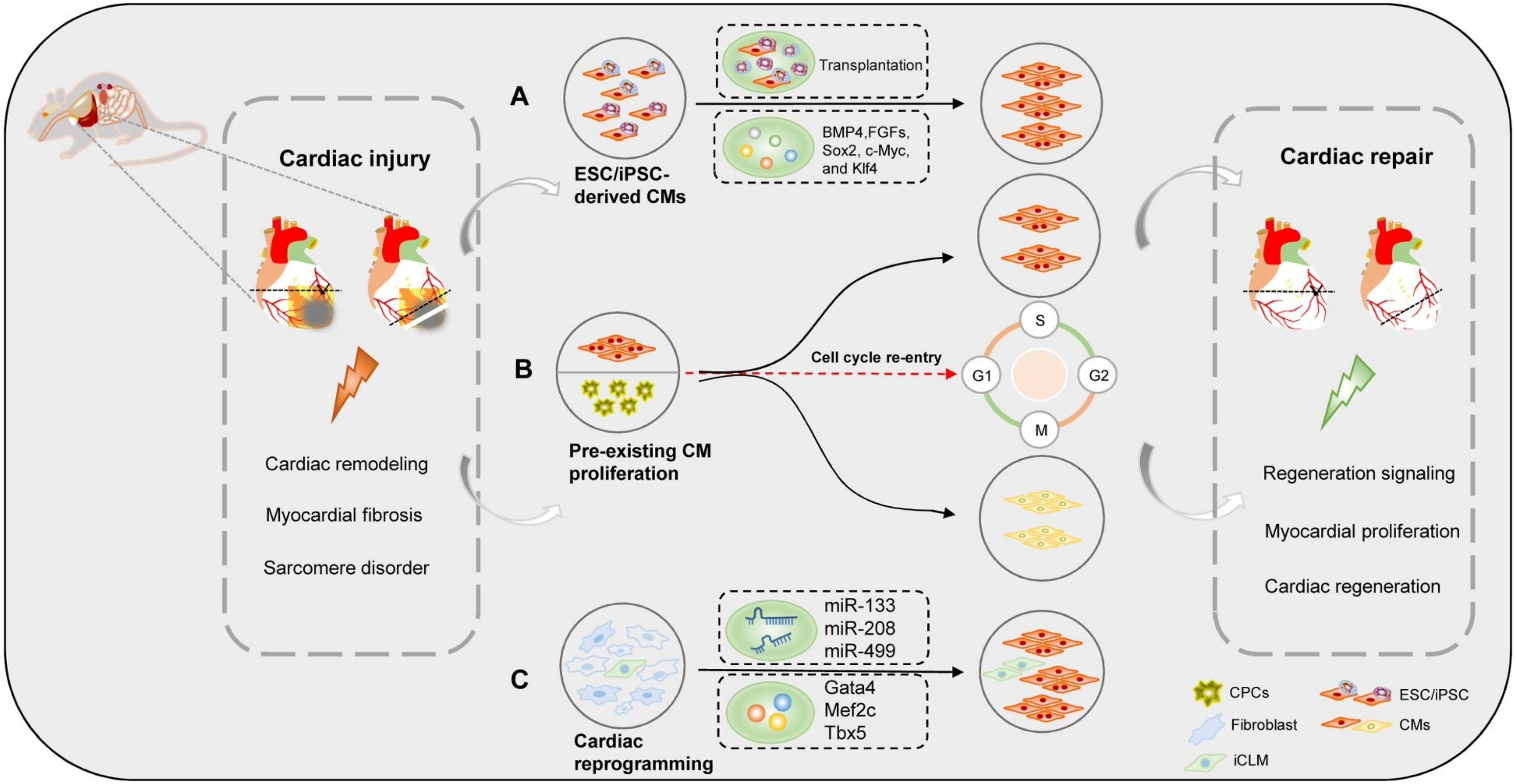
At least 64 million people worldwide suffer from Heart Failure

We have treatments, not cures.



Potential Cure = Regeneration to restore damaged heart tissue and function

Advances in Cardiac Regeneration

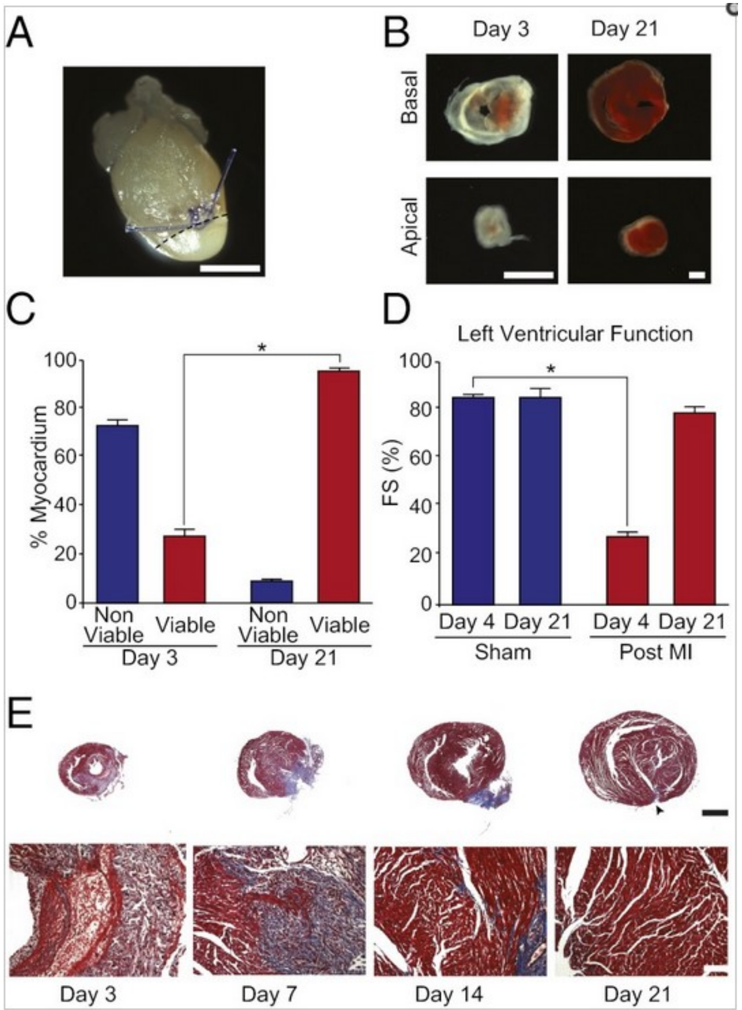


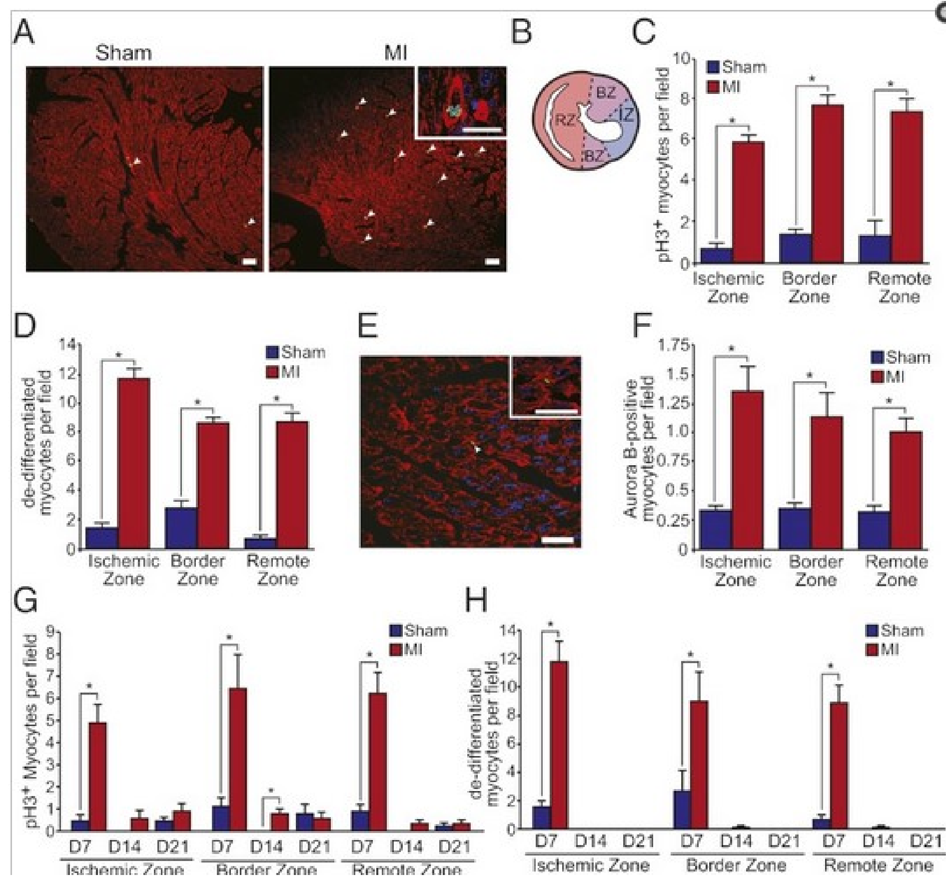
The discovery of endogenous cardiac regeneration

Genes & Diseases, 2024:11(2), 747-759.

Endogenous Cardiac Regeneration in mammals

The example of neonatal mouse heart



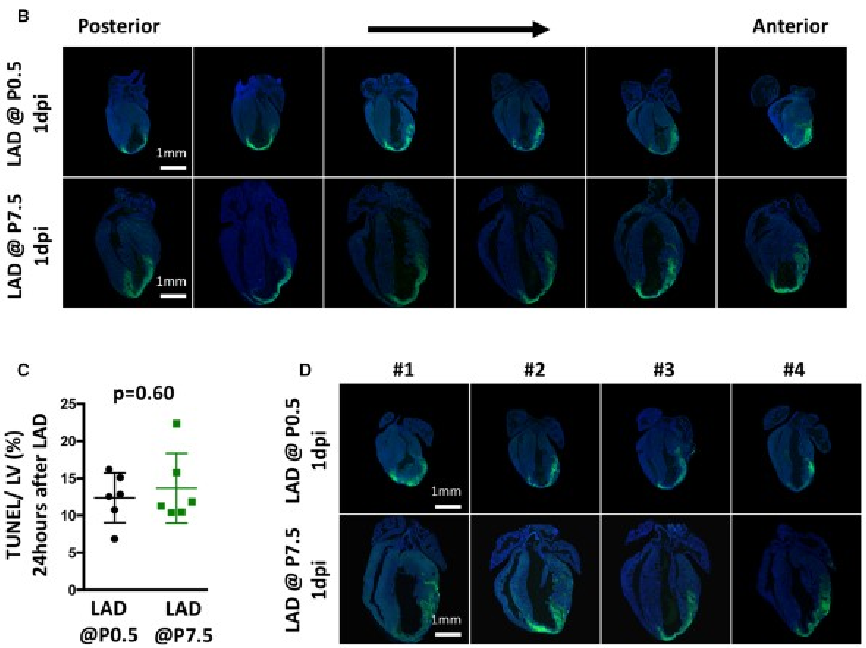


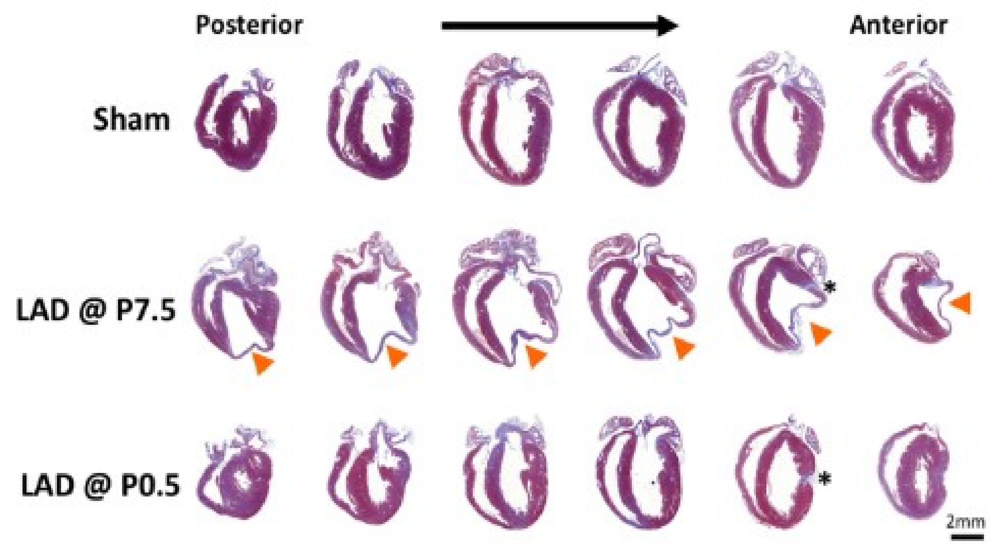
Within the first 7 days after birth

Porrello et al. Proc Natl Acad Sci U S A. 2013;110(1):187-92.

Endogenous Cardiac Regeneration in mammals

Neonatal heart: a conserved example of regeneration

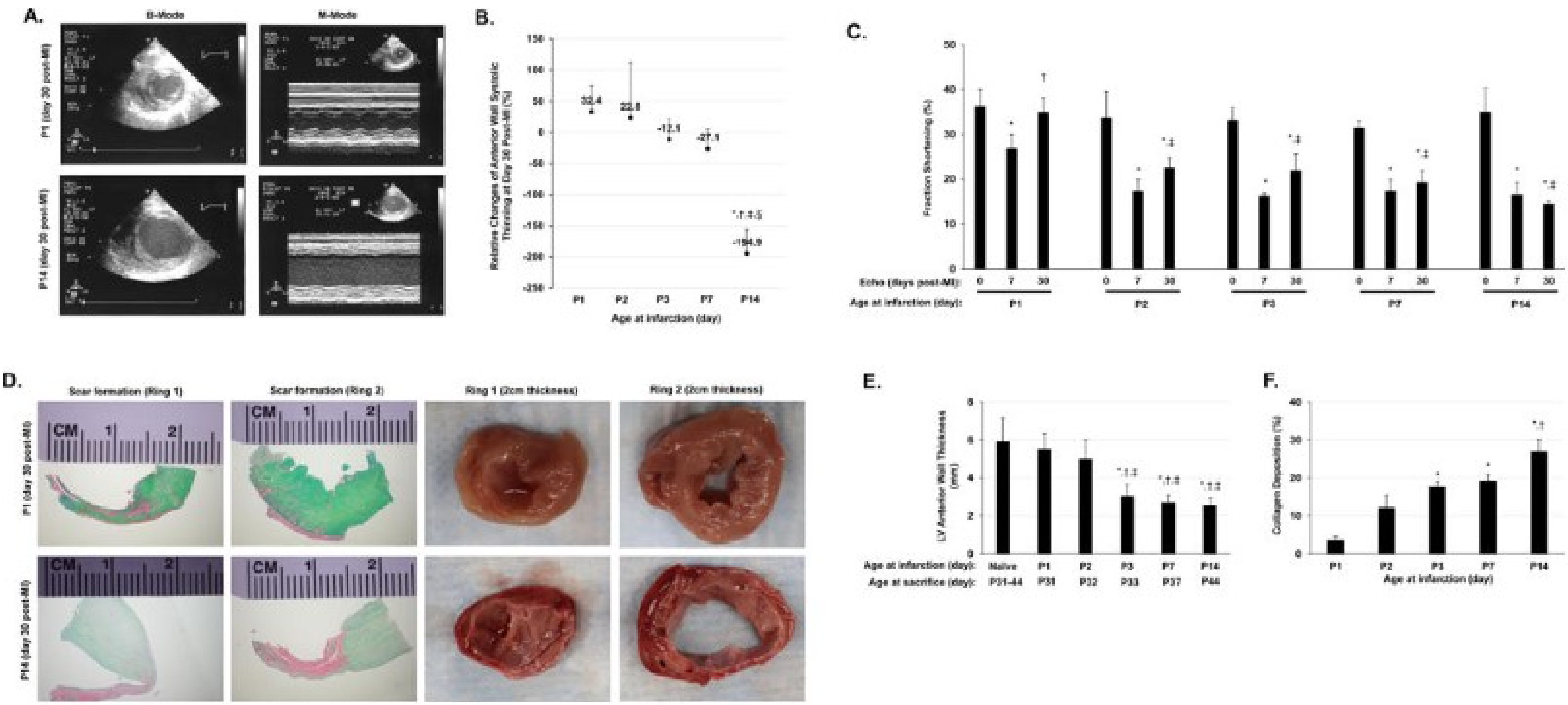




[Basic Res Cardiol.](#) 2016; 111(6): 64

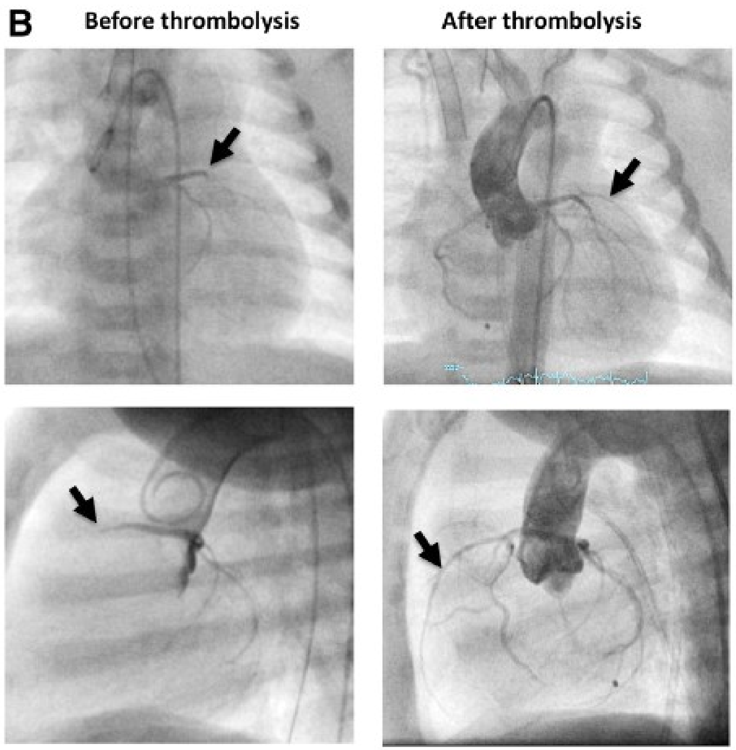
Regenerative Potential of Neonatal Porcine Hearts

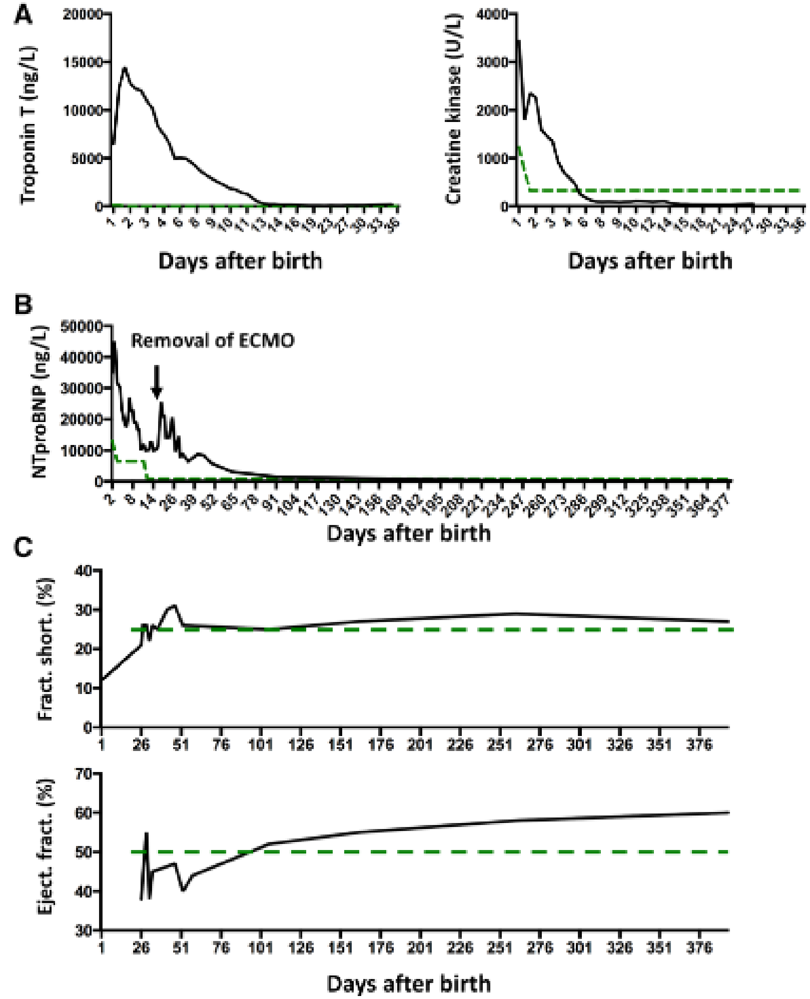
Neonatal heart: a conserved example of regeneration



Circulation. 2018 ; 138(24): 2809–2816

Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction

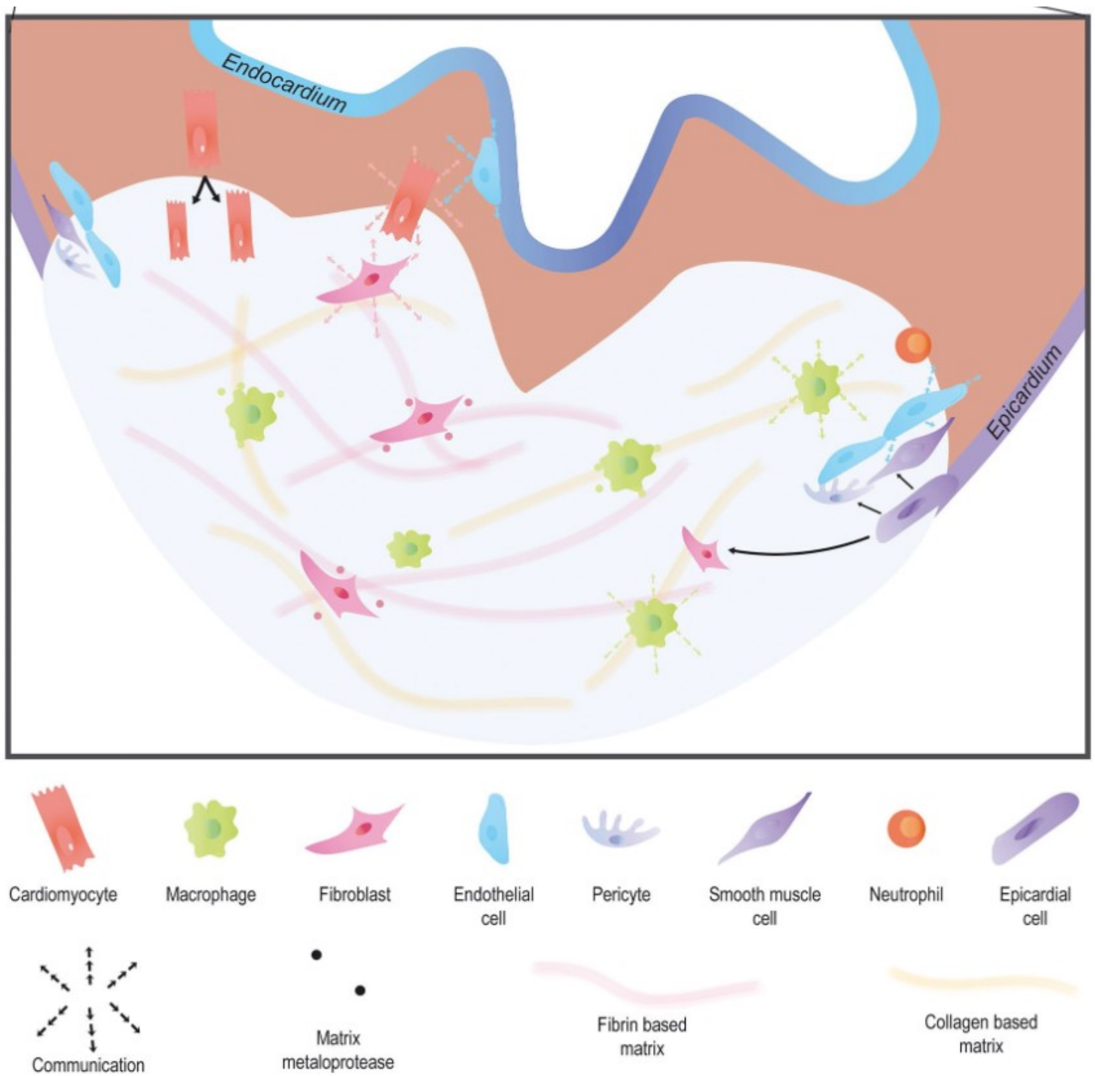




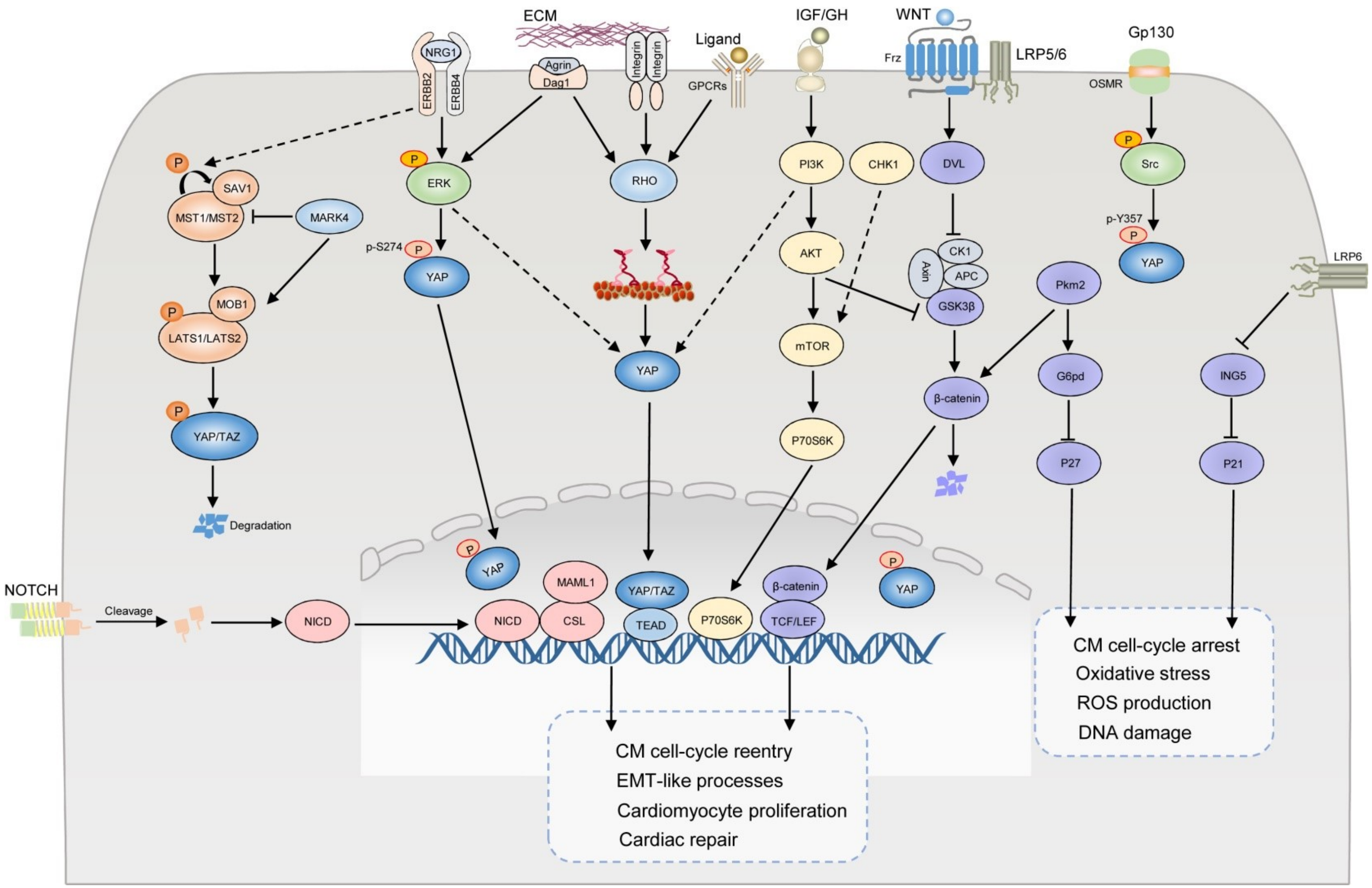
Circulation Research 2016; 118, Issue 2, Pages 216-221

Endogenous Cardiac Regeneration involves the integration of a multicellular response

Different type of cells are involved in the process of endogenous regeneration

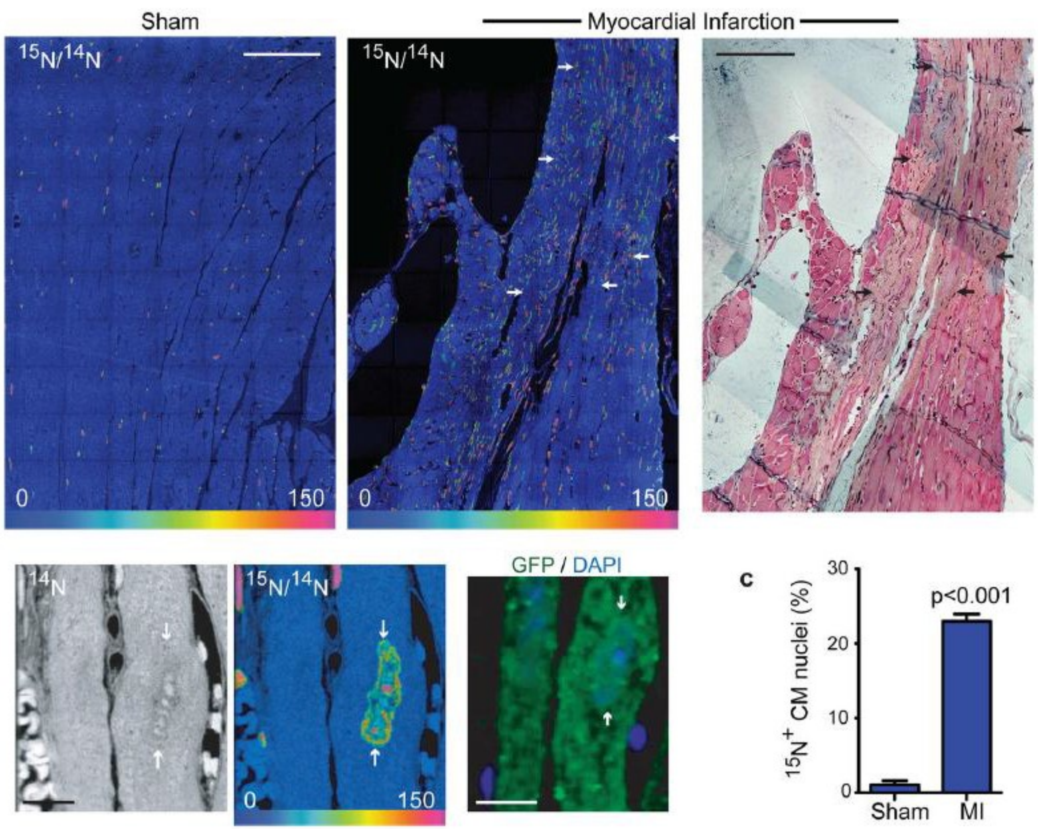


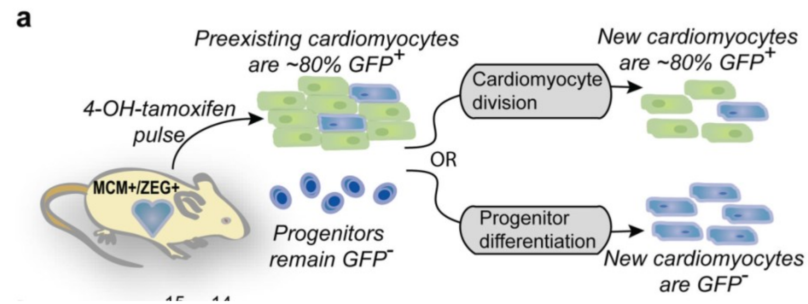
Molecular pathways involved in endogenous cardiac regeneration



Genes & Diseases, 2024:11(2), 747-759.

Endogenous regenerative capacity in adult mammalian heart





Cardiomyocyte nuclei in mitosis 23%

Final cell division – New cardiomyocytes 3.2% / 8 weeks

Senyo et al. 2013. Nature 493, 433-436

Important Conclusions

The capacity of Cardiac Regeneration in mammals exists

The program is activated or deactivated during development

The capacity of Cardiac Regeneration is based on a program that involves

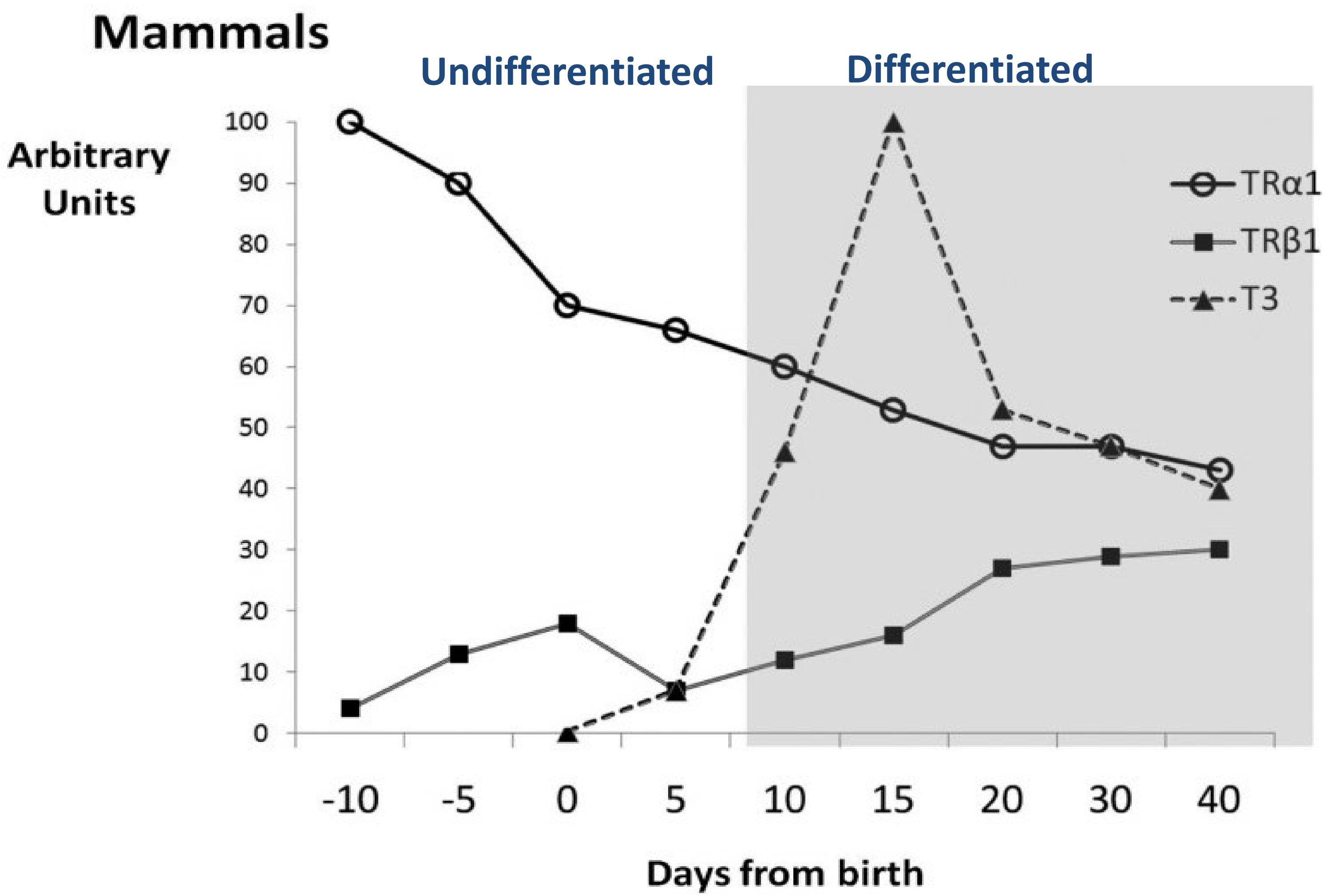
1. Dedifferentiation of surviving cardiomyocytes
2. Proliferation of surviving cardiomyocytes
3. Inhibition of proliferation
4. Re-Differentiation

Scientific Questions

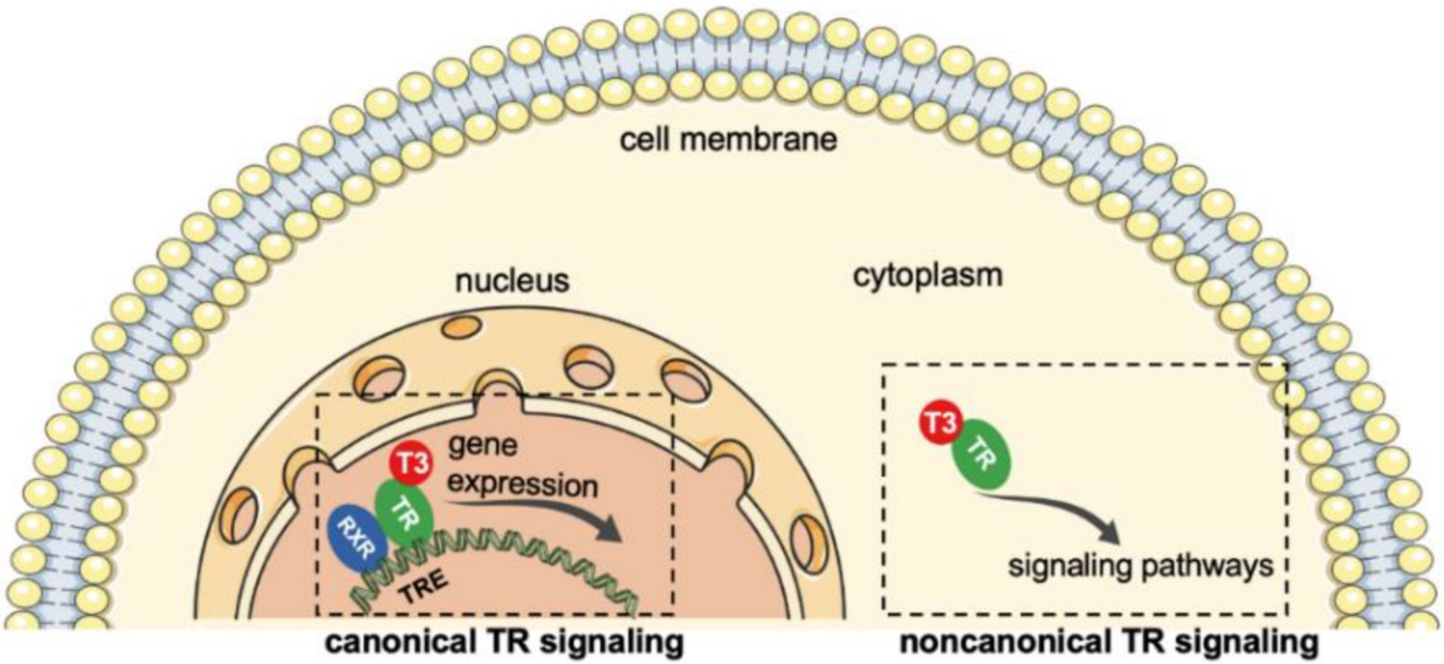
What is the main mechanism of activation and deactivation of the cardiac repair/regeneration program during development?

Can we regulate this program during myocardial injury to achieve cardiac repair/regeneration?

The Thyroid Hormone System is a key regulator of developmental processes in the heart of mammals

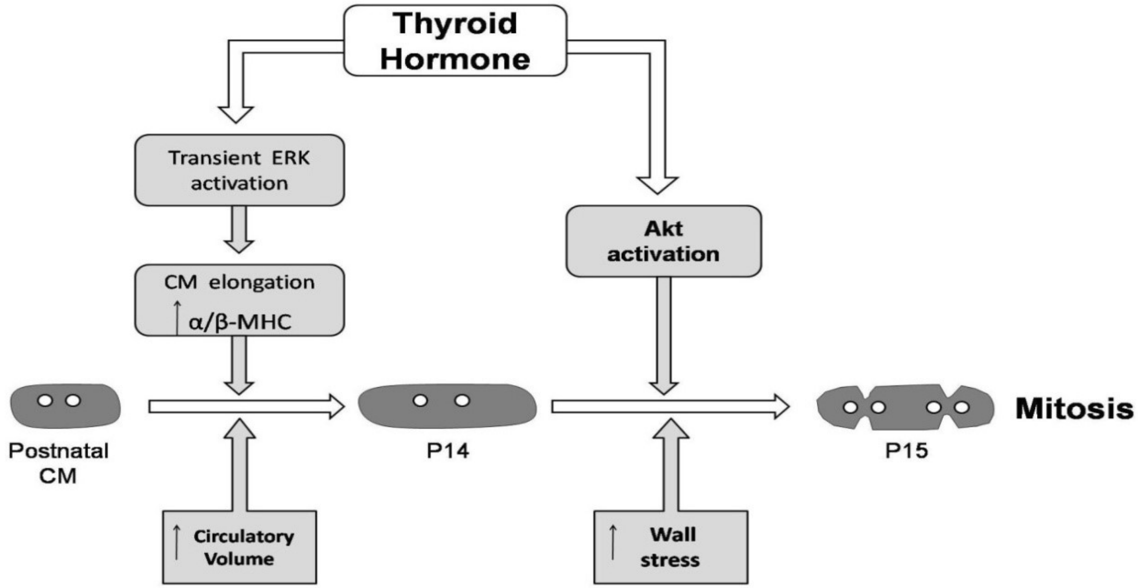


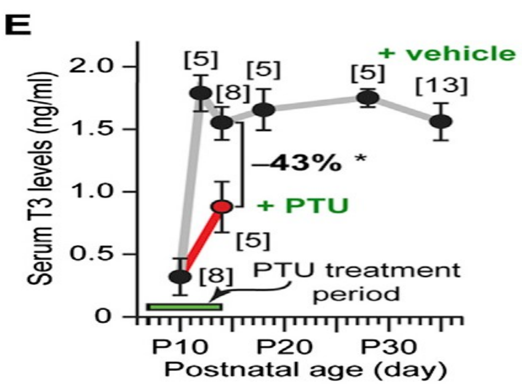
The Thyroid Hormone Signalling System

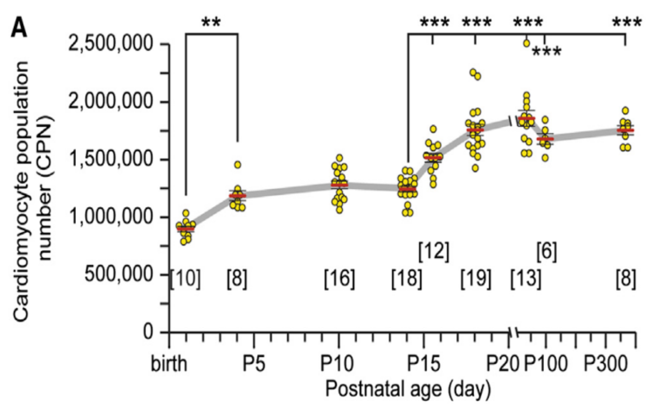


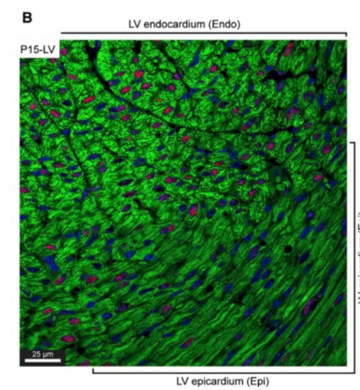
Int. J. Mol. Sci. **2022**, *23*(21), 13340

Developmental role of TH in cardiac growth beyond cell maturation in postnatal period





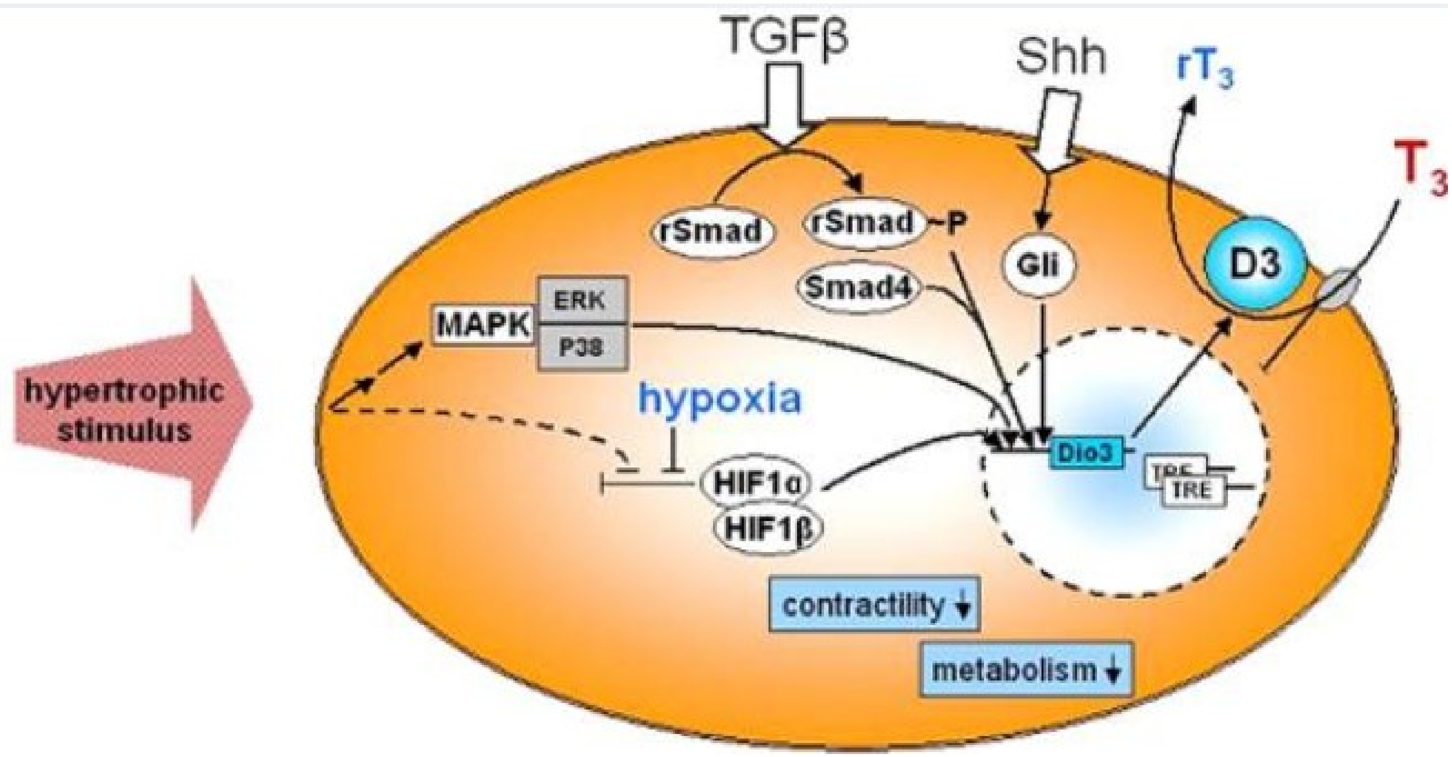




Pantos & Mourouzis Heart Fail Rev. 2015 May;20(3):273-82. Naqvi N et al, Cell. 2014, 8;157(4):795-807.

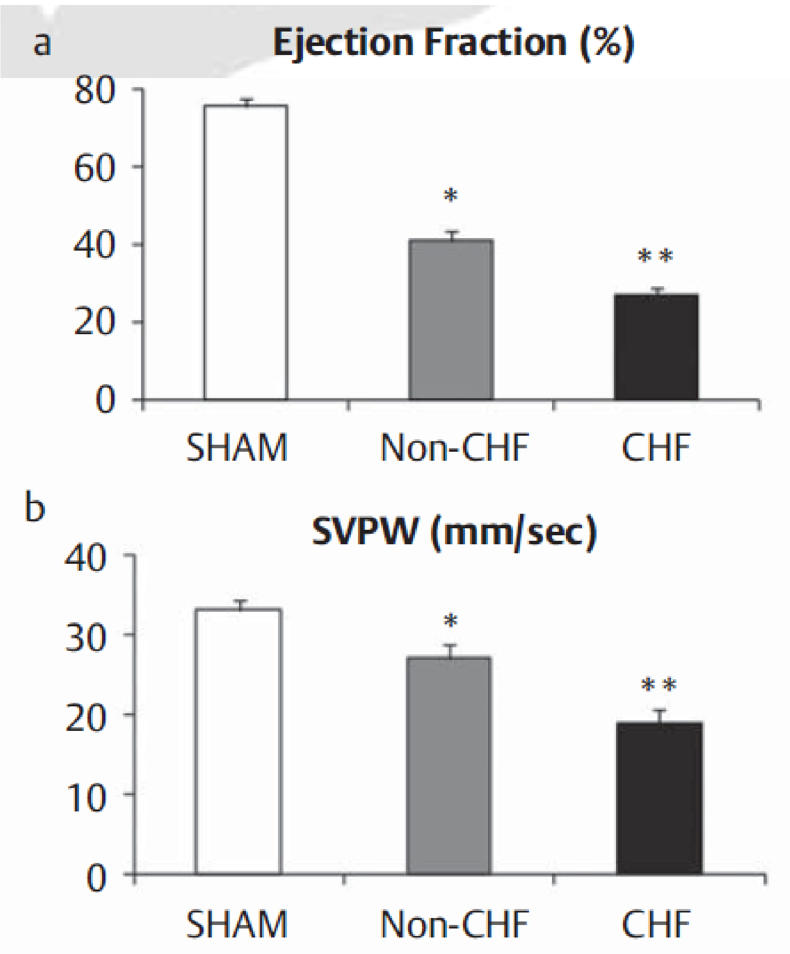
Pathophysiological role of TH signalling after myocardial ischemic stress

Pathophysiological changes in Thyroid Signalling after ischemic stress: Tissue levels of T3 drop

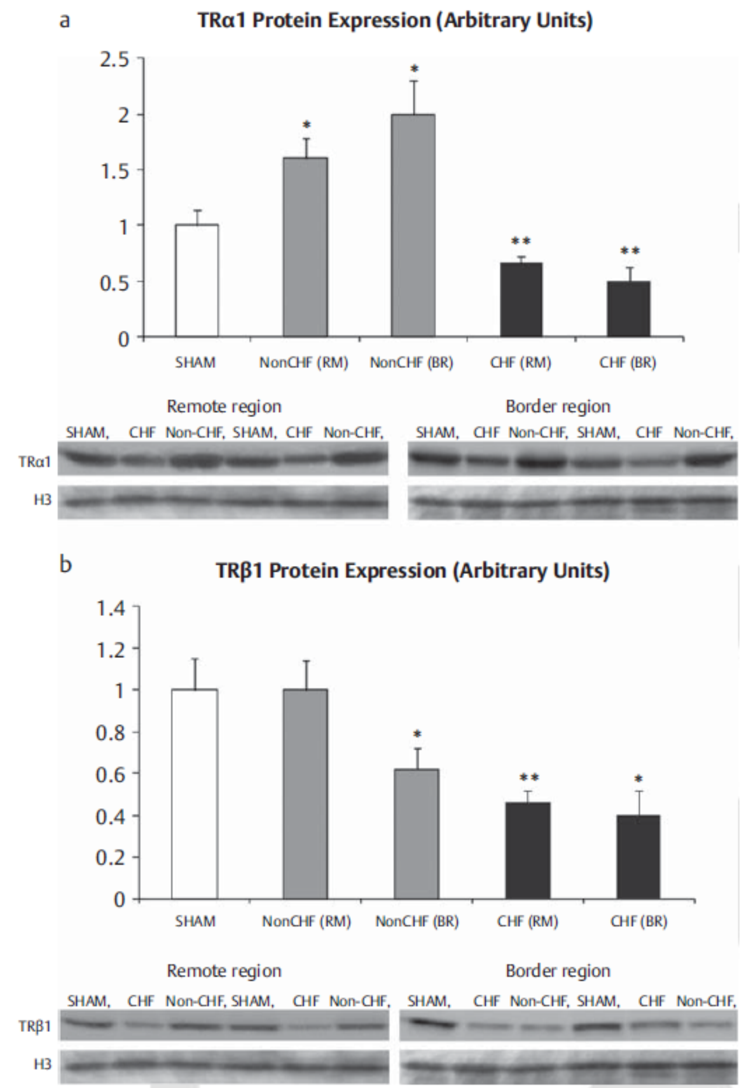


Janssen R, Muller A, Simonides WS (2017) Eur Thyroid J. 6: 130-137

Changes in Thyroid Hormone receptors after ischemic stress

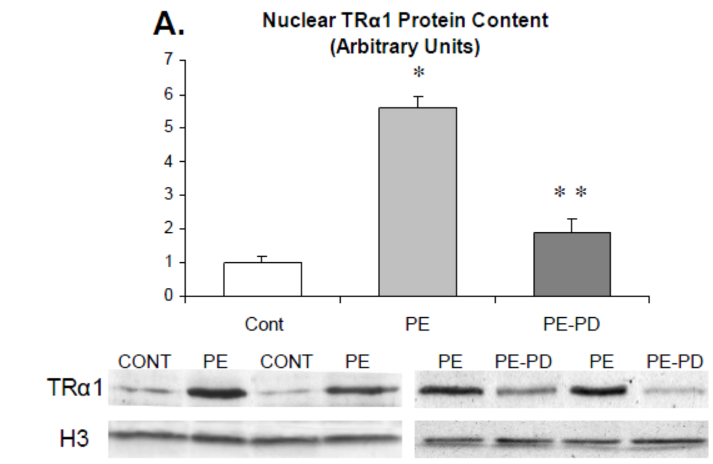


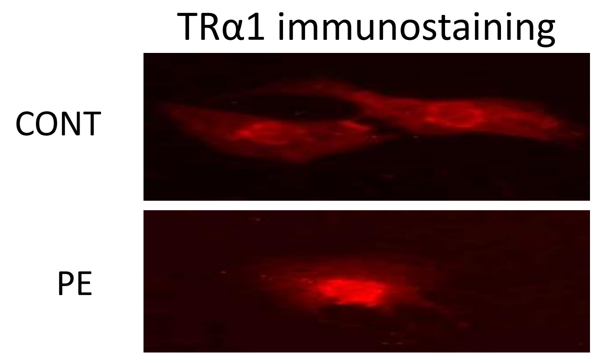
Nuclear Protein

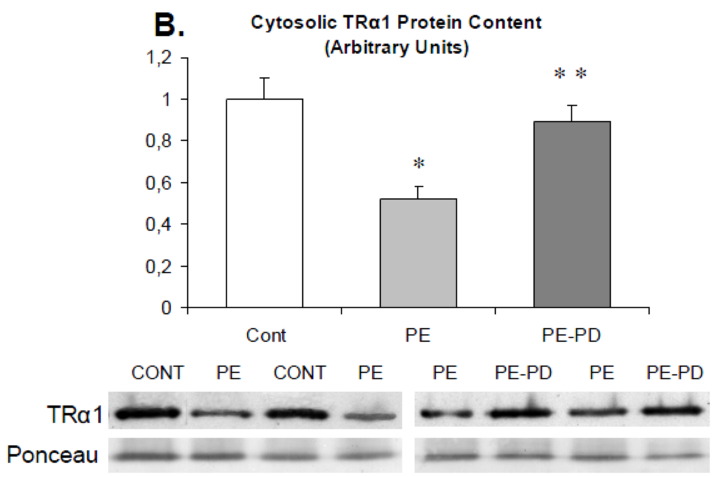


Pantos C, Mourouzis I et al, Horm Metab Res 2010; 42: 718 – 724

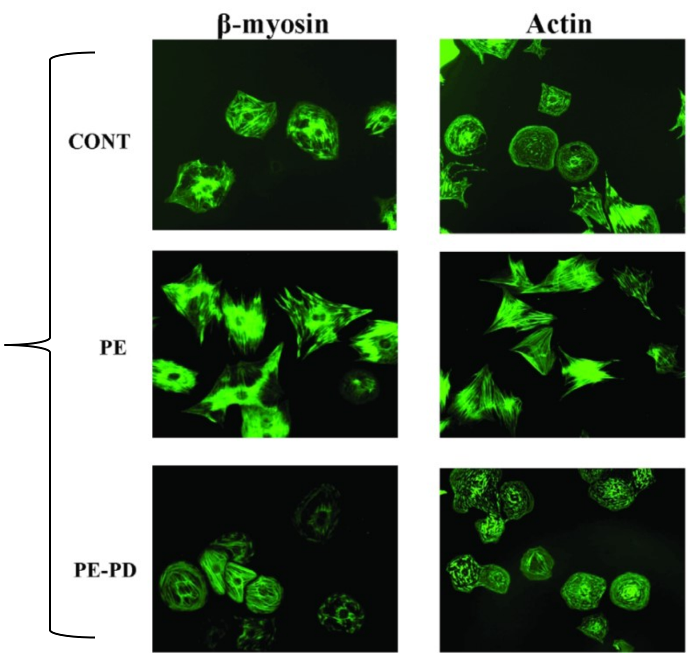
TRα1 redistribution to nucleus is regulated by stress signals (adrenergic stimulus): an ERK/mTOR dependent process





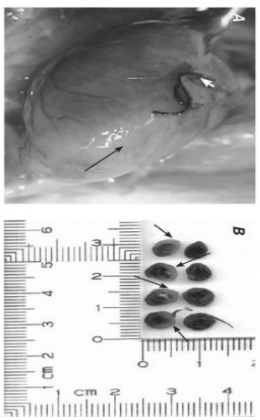


Without T3 in culture medium



Pantos C, Xinaris Ch et al , J Physiol Pharmacol. **2008** Jun;59(2):253-69.

Pharmacologic ‘knock out’ of TRα1 after Debutyl-dronedarone (DBD) treatment in mice with AMI results in deterioration of heart failure



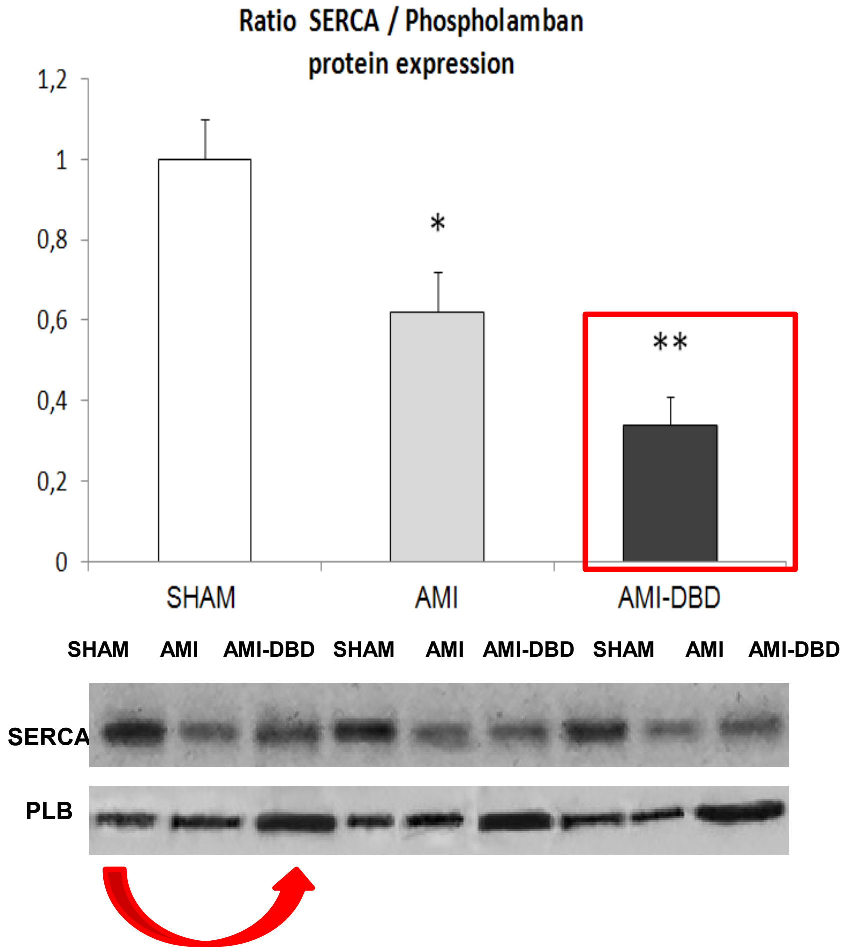
	SHAM $n = 9$	AMI $n = 11$	AMI–DBD $n = 15$
Heart rate (beats per min)	525(56)	473(35)	447(20)
LVIDd (mm)	3.3(0.12)	5.3 (0.23)*	5.4 (0.12)*
LVIDs (mm)	1.7(0.15)	4.4(0.24)*	4.8(0.13)*
EF%	79 (2.5)	33 (2.1)*	22 (1.1)$^{+}$
SVPW (mm/sec)	3.0(0.18)	2.0(0.15)*	1.7(0.15)*
LVPW (mm)	0.78 (0.01)	0.93 (0.03)*	0.75 (0.04)**
WTI	2.1(0.1)	2.9(0.12)*	3.7(0.22)$^{+}$
Sphericity Index	2.01(0.15)	1.63(0.07)*	1.67(0.04)$^{\&}$

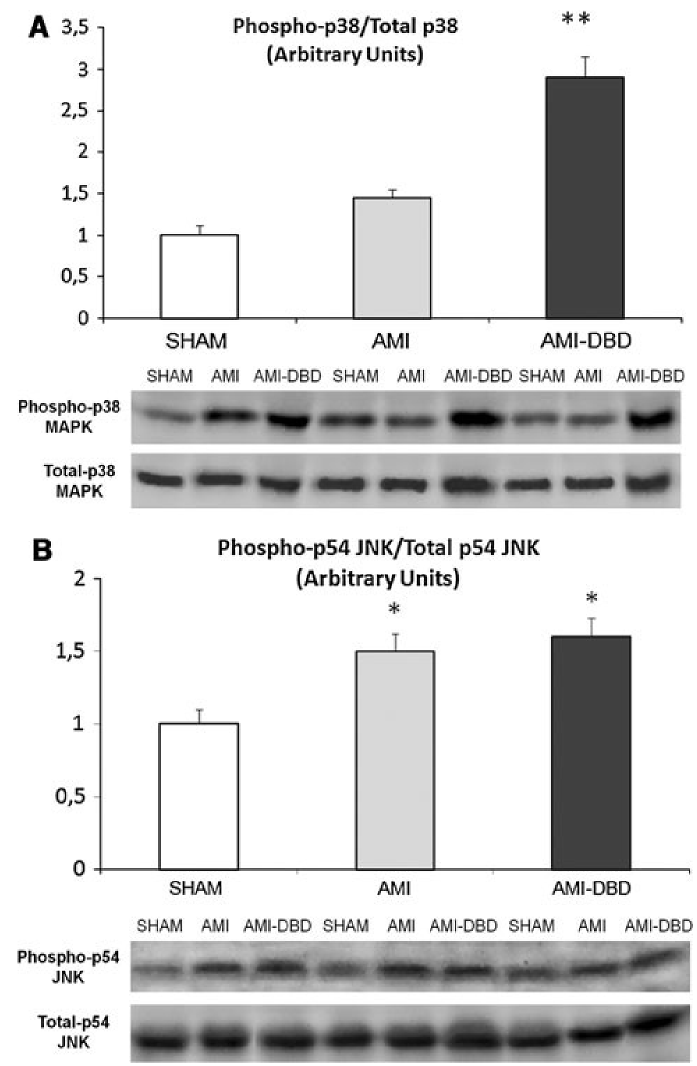
Mice were killed 3 weeks after MI. The values are mean (S.E.M)

* $p < 0.05$ versus SHAM, $^{+}p < 0.05$ versus SHAM and AMI, ** $p < 0.05$ versus AMI

Mourouzis et al, Mol Cell Biochem. **2013** Jul;379(1-2):97-105

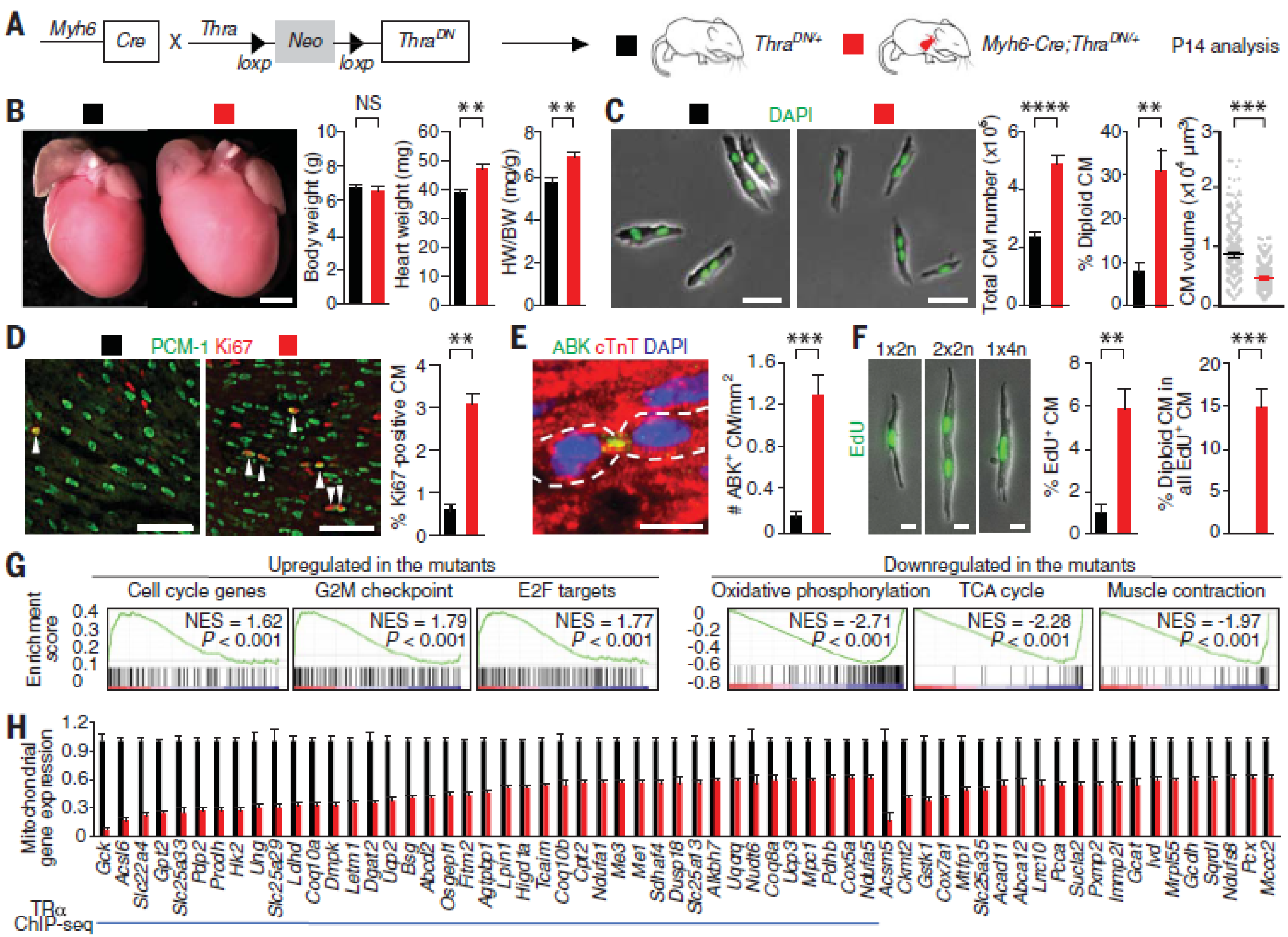
Pharmacologic 'knock out' of TRα1 results in dedifferentiation and increased apoptotic signaling





Mourouzis et al, Mol Cell Biochem. **2013** Jul;379(1-2):97-105

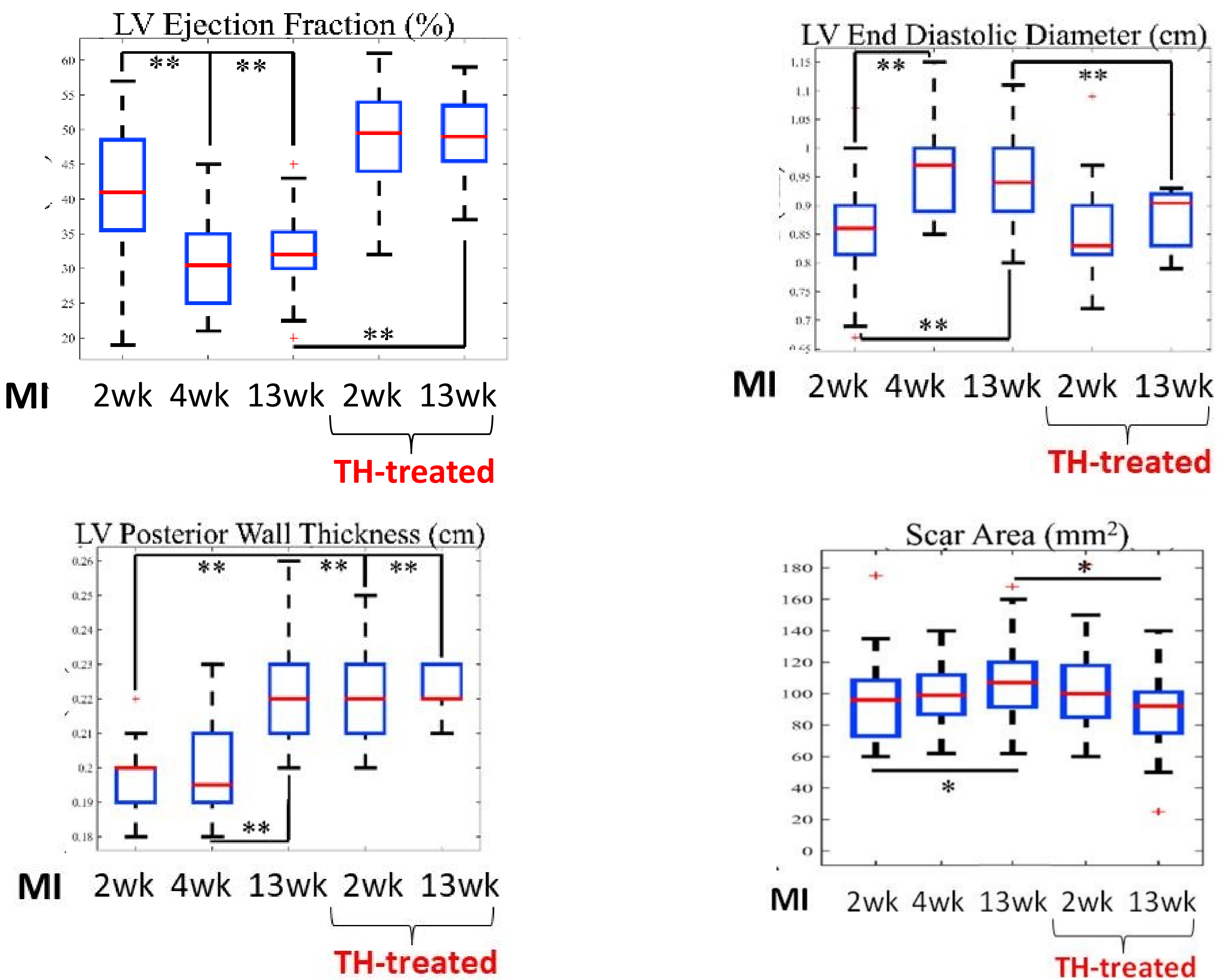
Overexpression of CM-specific mutant TRα1 enhances proliferation in neonatal mice but inhibits differentiation



Hirose et al., Science 364, 184–188 (2019)

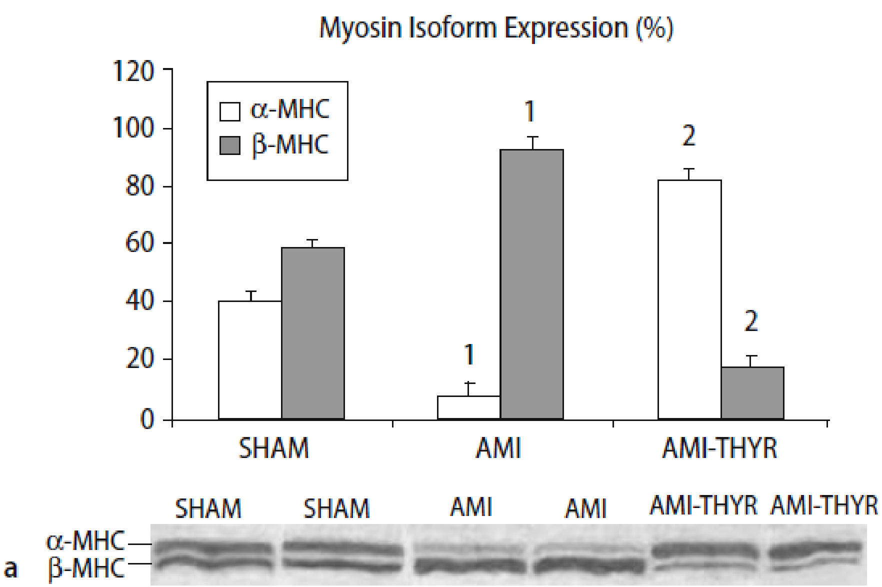
Therapeutic role of TH signalling after myocardial ischemic stress

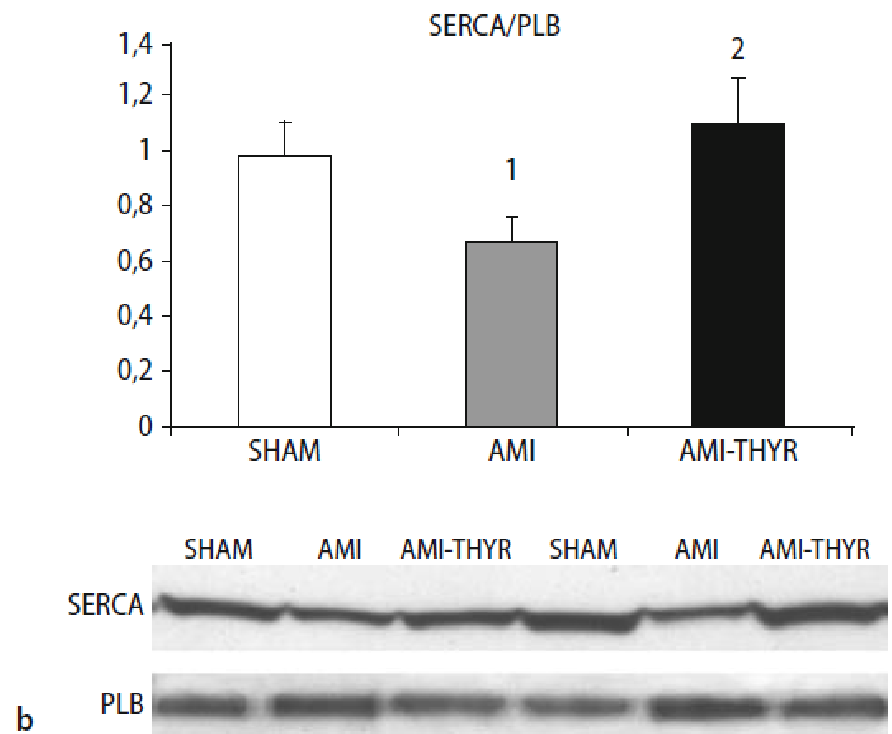
TH treatment after myocardial infarction (MI) in rats increases cardiac mass, improves LV function and inhibits cardiac remodeling



Iliopoulou I, Mourouzis I et al, Mol Med Rep. 2018 Jul;18(1):864-876.

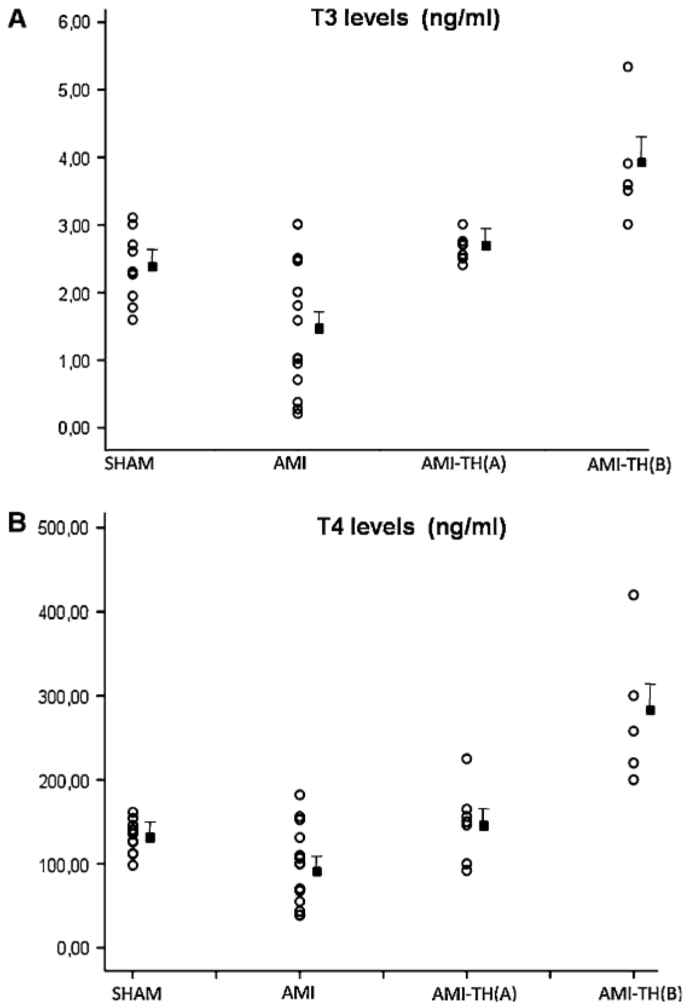
TH treatment after MI results to differentiated cardiac mass





Pantos C, Mourouzis I et al. Basic Res Cardiol. 2008 Jul;103(4):308-18.

Long-term treatment with TH after myocardial infarction in mice can improve myocardial remodelling and function



	SHAM	AMI	AMI-TH (A)	AMI-TH (B)
Heart rate (beats per min)	550 (30)	495 (38)	460 (29)	450 (25)
LVIDd (mm)	3.5 (0.09)	6.0 (0.13)*	5.1 (0.16)$^{+}$	5.6 (0.18)*
LVIDs (mm)	2.0 (0.11)	5.3 (0.15)*	4.2 (0.20)$^{+}$	4.6 (0.32)*
EF%	78 (1.9)	27.9 (1.4)*	38.0 (3.1)$^{+}$	29 (3.7)*
SVPW (mm/sec)	3.0 (0.13)	1.5 (0.12)*	2.2 (0.2)$^{+}$	1.8 (0.19)*
LVW/BW	3.0 (0.1)	4.0 (0.2)*	4.1 (0.3)*	5.0 (0.45)$^{+}$
WTI	1.56 (0.07)	3.2 (0.16)*	2.6 (0.24)$^{+}$	2.8 (0.14)*
Sphericity index	1.9 (0.08)	1.43 (0.03)*	1.67 (0.06)$^{\&}$	1.6 (0.09)

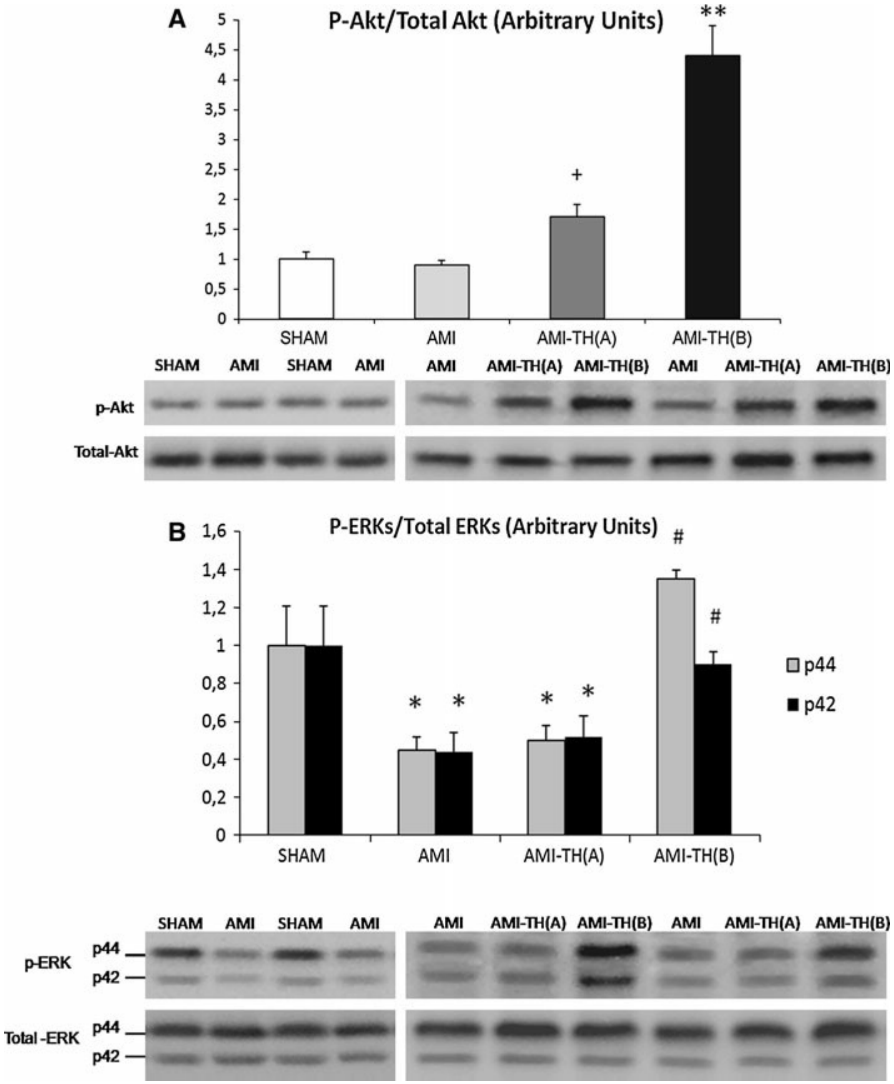
The values are mean (S.E.M)

* $P < 0.05$ vs SHAM

$^{+}$ $P < 0.05$ vs SHAM and AMI

$^{\&}$ $P = 0.08$ vs AMI

Chronic changes in kinase signaling activation after TH treatment



TH treatment affects AKT and ERK signaling in a dose-dependent manner

Mourouzis et al. Mol Cell Biochem. 2012 Apr;363(1-2):235-43.

<u>Novel Concept</u>

Mimic the pattern of TH changes after birth.

High T3 levels for a short period of time

Dose-dependent effects of acute triiodothyronine administration in an *in vivo* model of ischemia-reperfusion in rats

Acute, high dose T3 blocks heart dilatation after myocardial infarction and reperfusion in rats

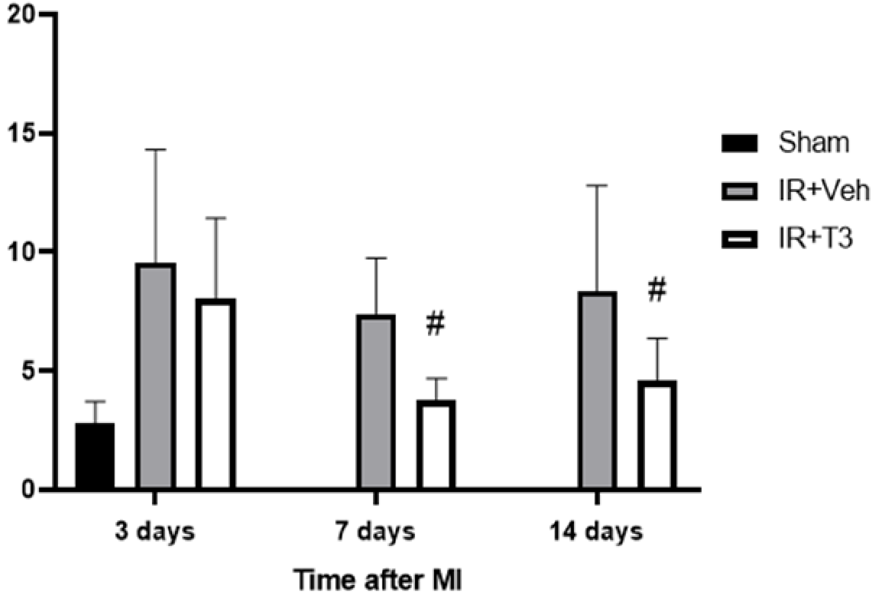
	ContIR (n=11)	T3(5)IR (n=8)	T3(10)IR (n=10)	T3(20)IR (n=11)	T3(40)IR (n=9)
LVIDd (mm)	7.0 (0.21)	7.6 (0.16)	7.5 (0.25)	6.2(0.25)**	7.3 (0.16)
LVIDs (mm)	4.5 (0.30)	5.7 (0.40)	5.3 (0.30)	3.7(0.20)**	4.3(0.20)
LVEF%	49.9 (1.6)	51.3 (2.5)	50.9 (2.1)	58.5 (1.8)*	61.2 (2.2)*
SVPW (mm/sec)	3.2 (0.21)	3.5 (0.11)	3.5 (0.10)	4.0 (0.24)	3.9 (0.15)
Scar Area (mm^2)	87 (5.4)	90 (3.6)	90 (5.4)	92 (4.5)	89 (6.7)

One-Way ANOVA was used for multiple comparisons between groups. Post-hoc tests were performed with Bonferroni or Dunett's T3 correction.

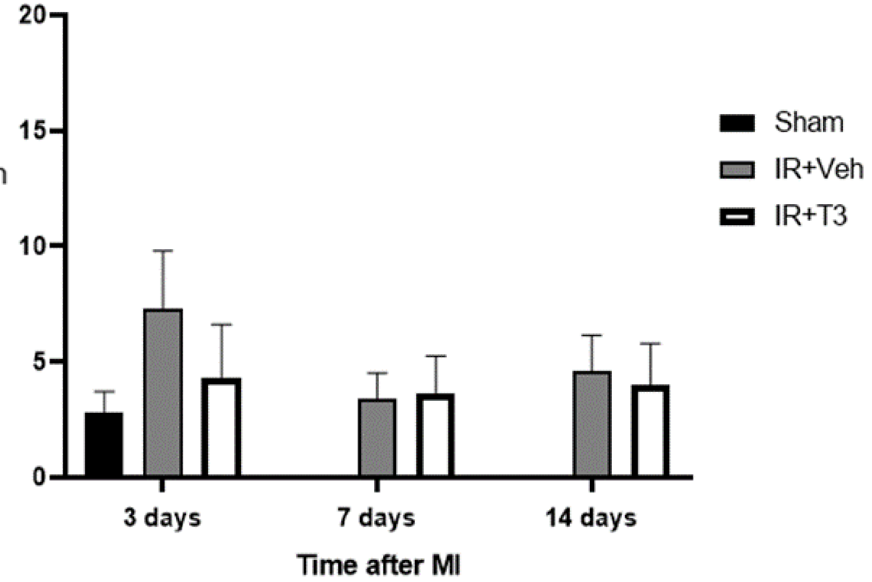
* $p<0.05$ vs ContIR group ** $p<0.01$ vs T3(5)IR and T3(10)IR group,

Acute, high dose T3 decreases fibrosis

A Percentage of myocardial tissue with injury, fibrosis and infiltration (%) - BR

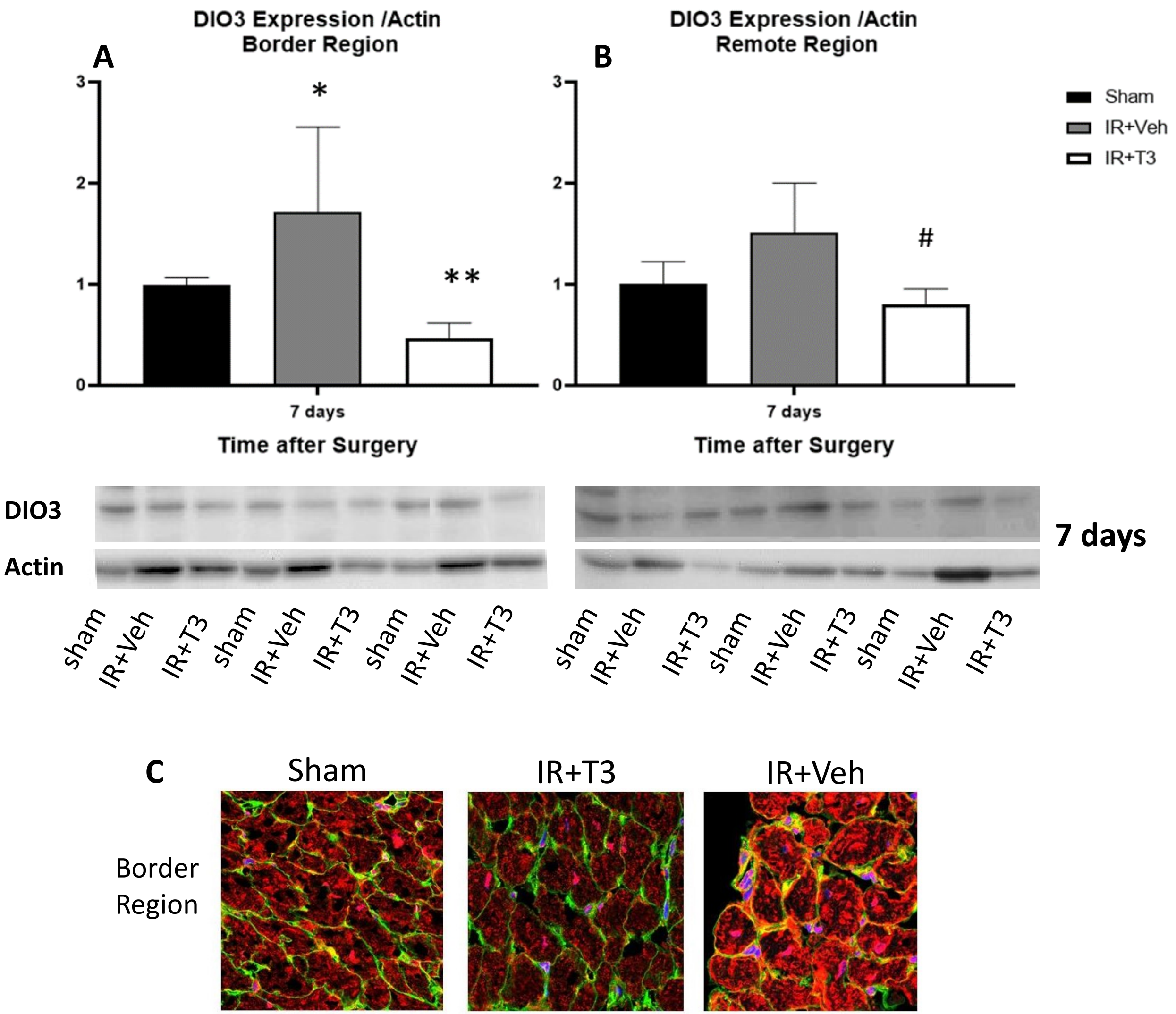


B Percentage of myocardial tissue with injury, fibrosis and infiltration (%) - RR



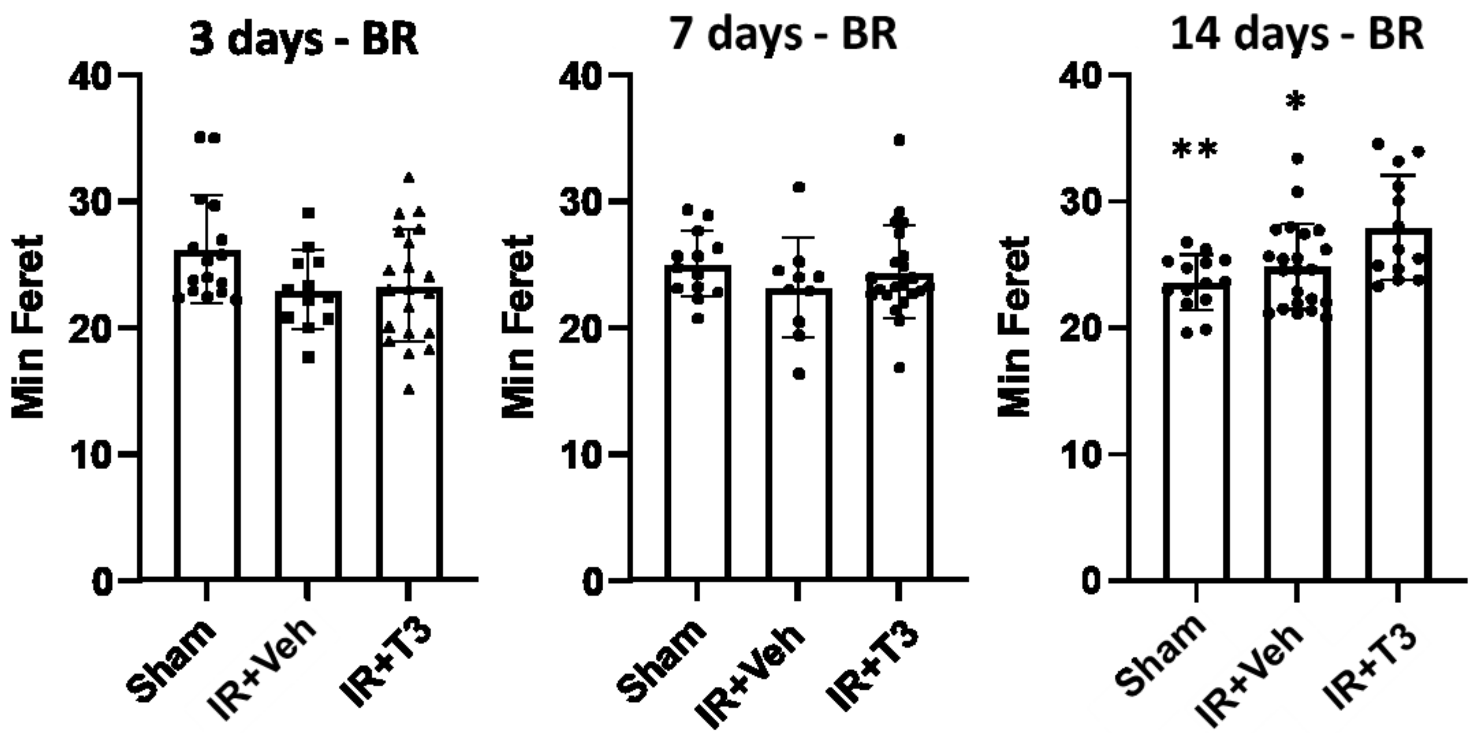
Unpublished data

Acute, high dose T3 inhibits tissue hypothyroidism



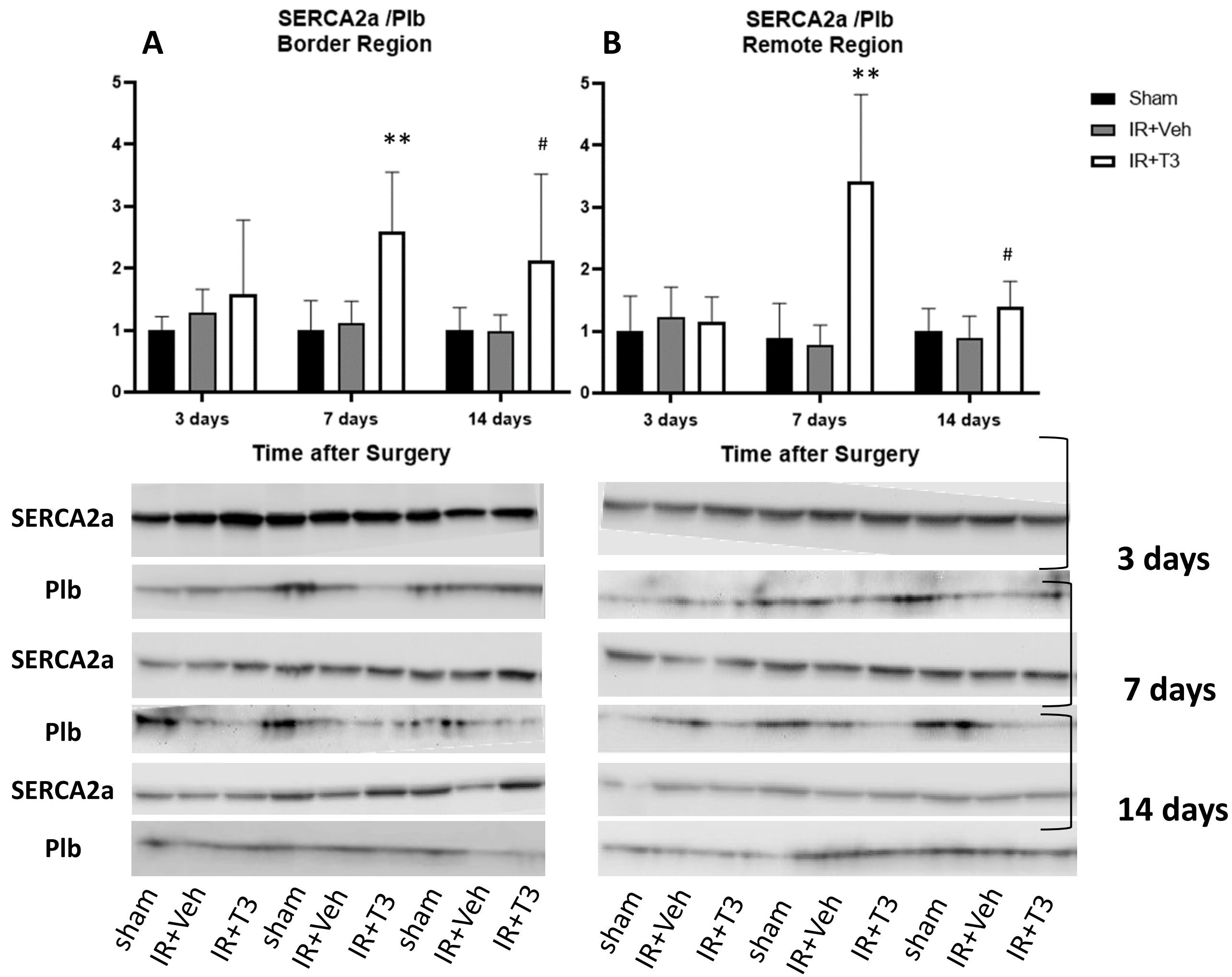
Unpublished data

Acute, high dose T3 causes cardiomyocyte hypertrophy



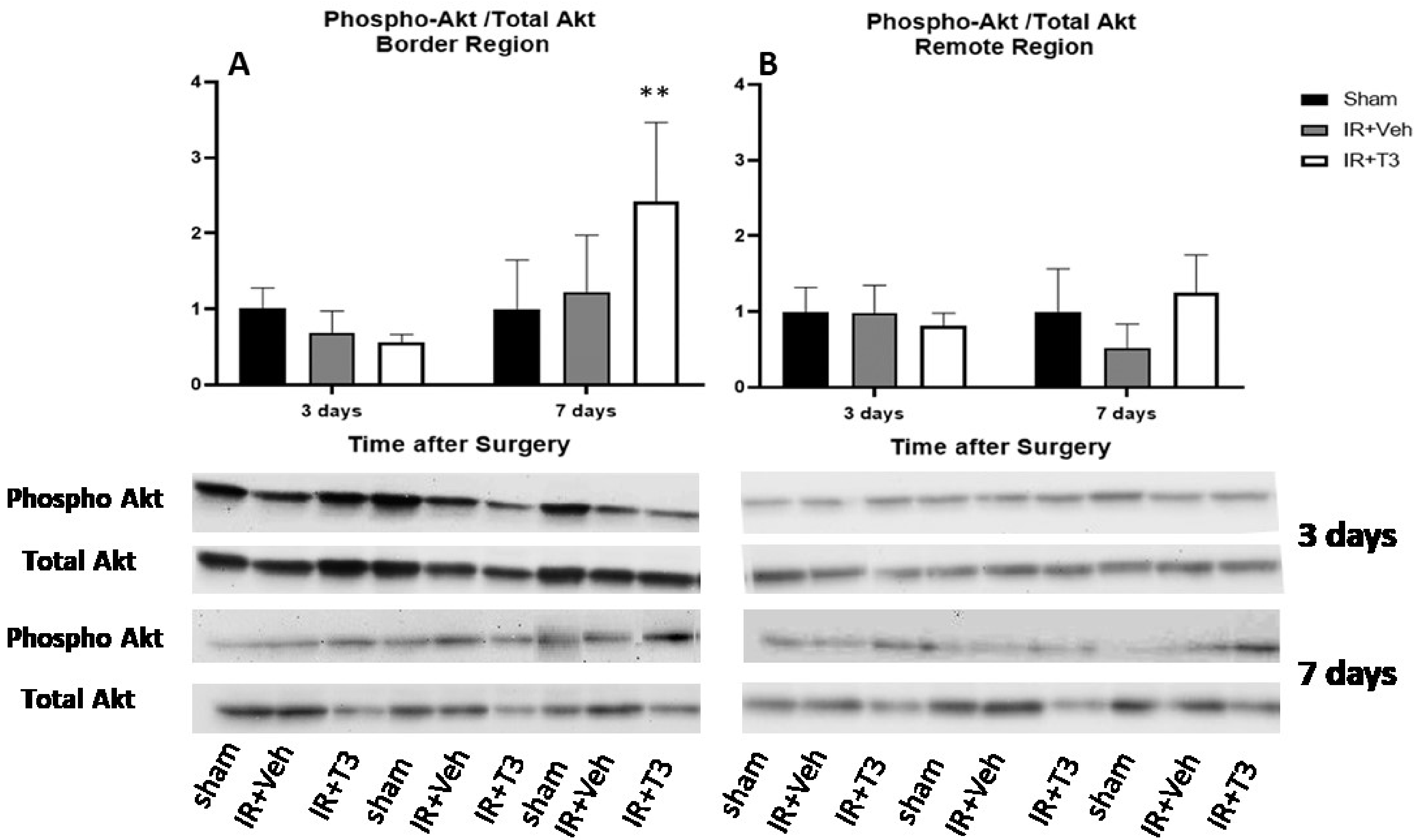
Unpublished data

Acute, high dose T3 induces differentiation of postinfarcted myocardium



Unpublished data

Acute, high dose T3 induces Akt activation



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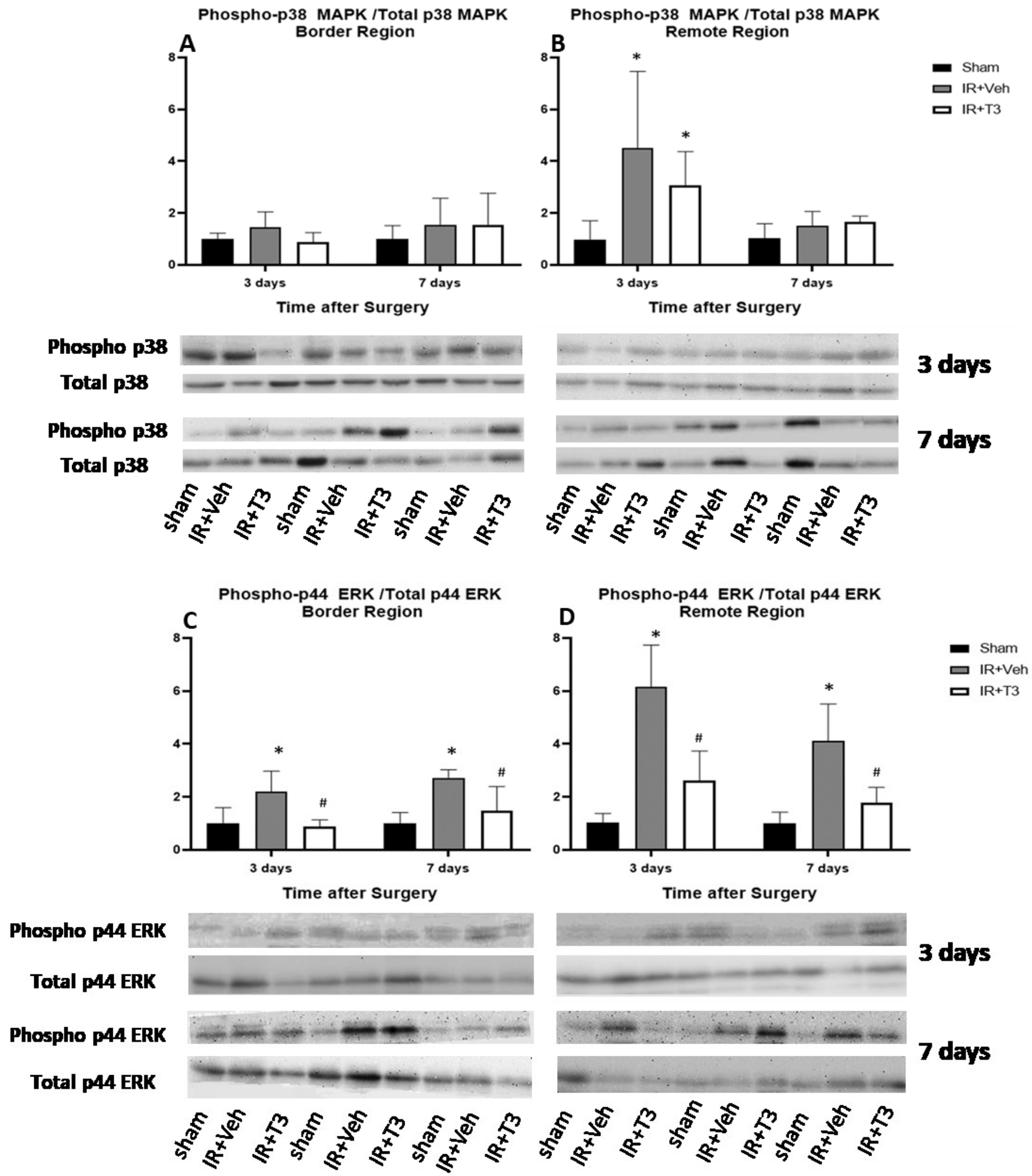
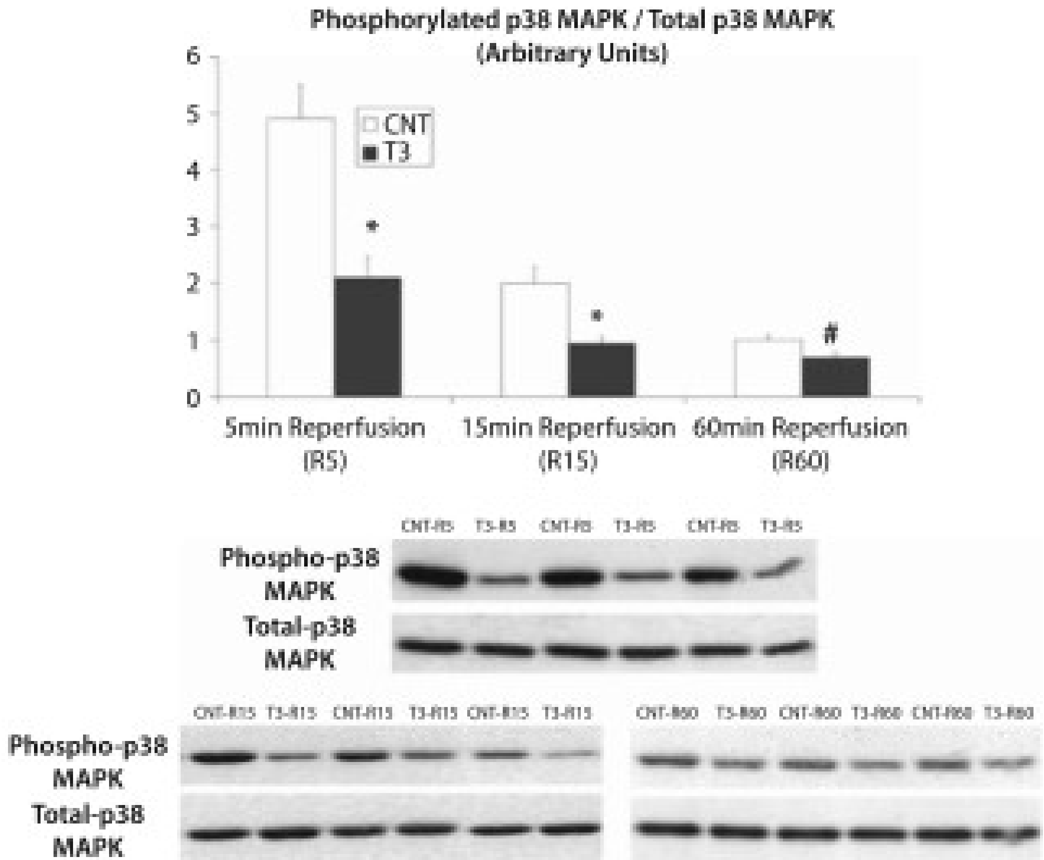


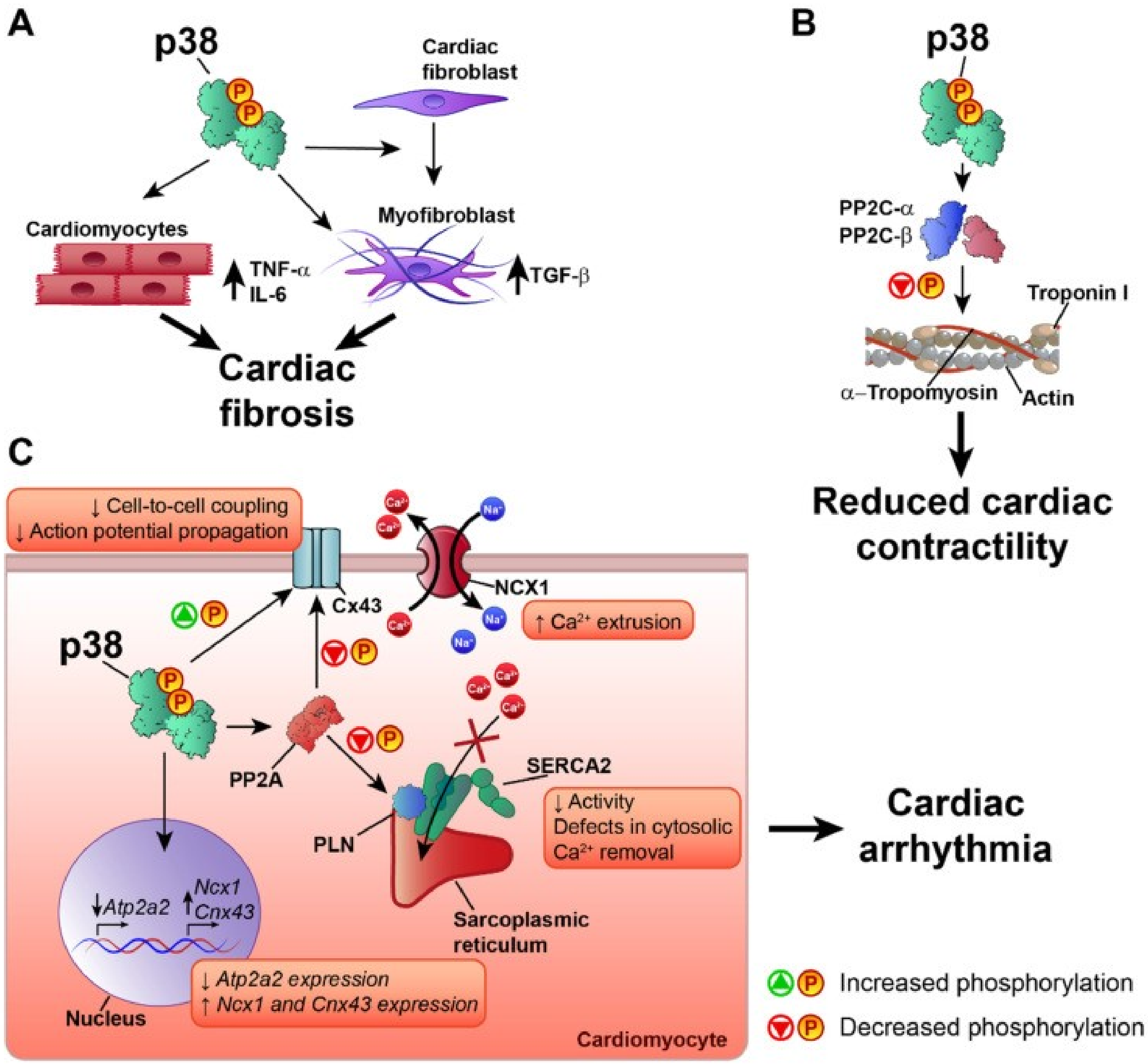
Unpublished data

Acute changes in kinase signaling activation after TH treatment



Pantos C, Mourouzis I et al , Basic Res Cardiol. 2009 Jan;104(1):69-77

Role of p38 MAPK in cardiac remodeling



Int J Mol Sci. 2020 Oct; 21(19): 7412

Clinical Translation Phase IIa Study

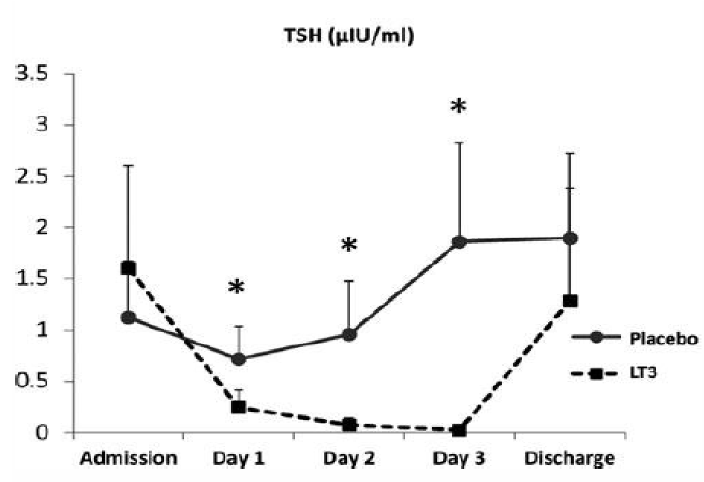
Effects of Acute Triiodothyronine Treatment in Patients with Anterior Myocardial Infarction Undergoing Primary Angioplasty: Evidence from a Pilot Randomized Clinical Trial (ThyRepair Study)

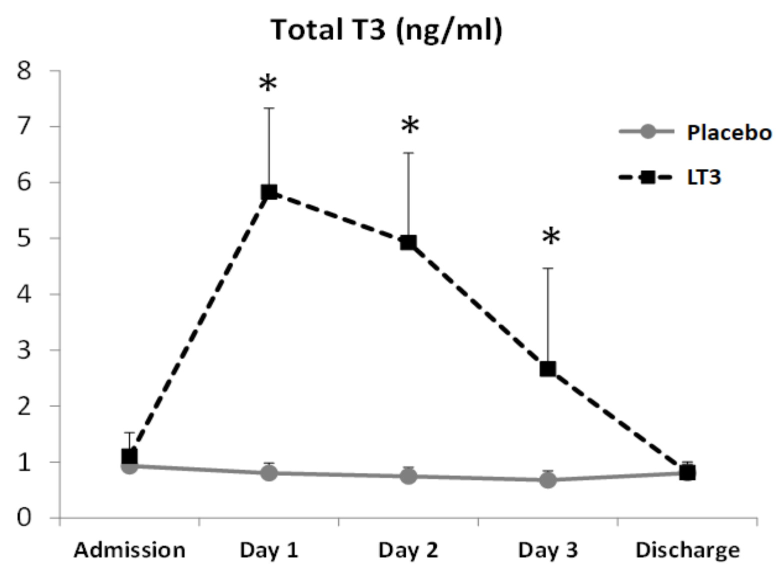
Constantinos I. Pantos,[1] Athanasios G. Trikas,[2] Evangelos G. Pissimisis,[3] Konstantinos P. Grigoriou,[2] Pavlos N. Stougiannos,[2] Antonios K. Dimopoulos,[3] Sarantos I. Linardakis,[3] Nikolaos A. Alexopoulos,[4,5] Costas G. Evdoridis,[2] Gerasimos D. Gavrielatos,[2] Nikolaos G. Patsourakos,[3] Nikolaos D. Papakonstantinou,[3] Anastasios D. Theodosis-Georgilas,[3] and Iordanis S. Mourouzis[1]

THYROID
Volume 32, Number 6, 2022

Dosage Scheme

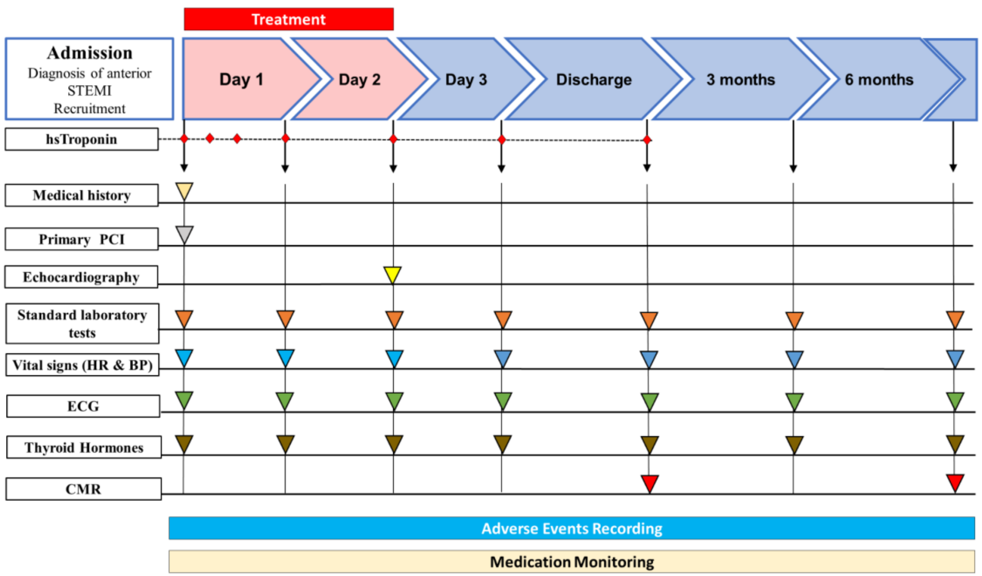
Patient weight	Bolus administration	Continuous infusion per 24 hours – pump rate	
66 Kg	5.5 mL (55 μg) over 2-3 min	18 mL (180 μg) in 232 mL NaCl 0.9%	10.4 mL/h
70 Kg	5.5 mL (55 μg) over 2-3 min	19 mL (190 μg) in 231 mL NaCl 0.9%	10.4 mL/h
74 Kg	6 mL (60 μg) over 2-3 min	20 mL (200 μg) in 230 mL NaCl 0.9%	10.4 mL/h
77 Kg	6 mL (60 μg) over 2-3 min	21 mL (210 μg) in 229 mL NaCl 0.9%	10.4 mL/h
81 Kg	6.5 mL (65 μg) over 2-3 min	22 mL i(220 μg) n 228 mL NaCl 0.9%	10.4 mL/h
85 Kg	7.0 mL (70 μg) over 2-3 min	23 mL (230 μg) in 227 mL NaCl 0.9%	10.4 mL/h
89 Kg	7.0 mL (70 μg) over 2-3 min	24 mL (240 μg) in 226 mL NaCl 0.9%	10.4 mL/h
92 Kg	7.5 mL (75 μg) over 2-3 min	25 mL (250 μg) in 225 mL NaCl 0.9%	10.4 mL/h
>95 Kg	7.5 mL (75 μg) over 2-3 min	26 mL (260 μg) in 224 mL NaCl 0.9%	10.4 mL/h

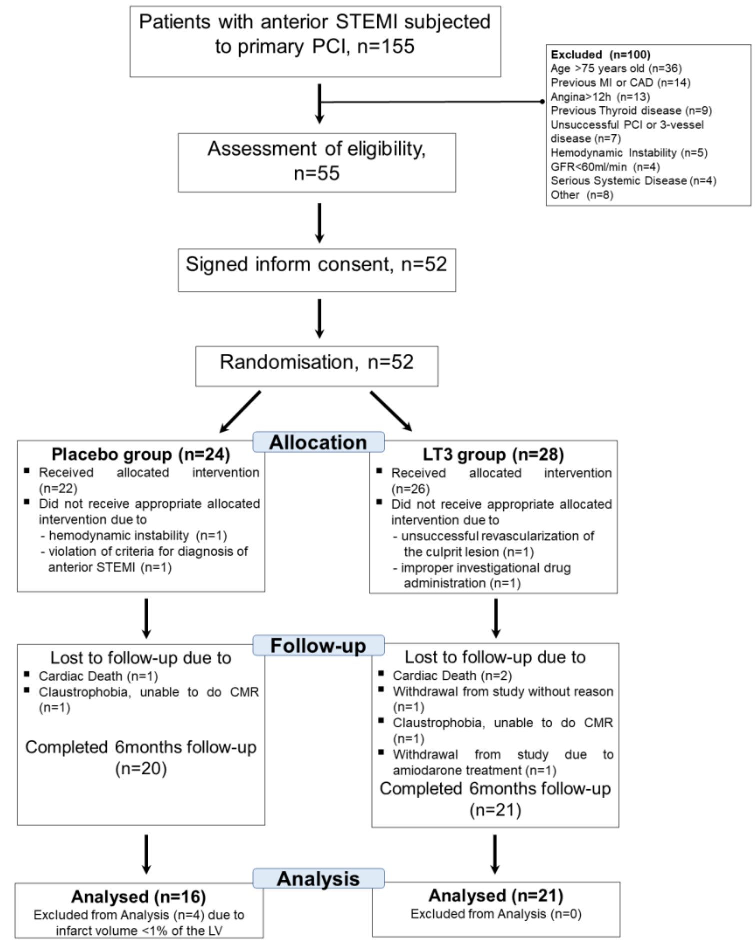




Thyroid. 2022 Jun;32(6):714-724

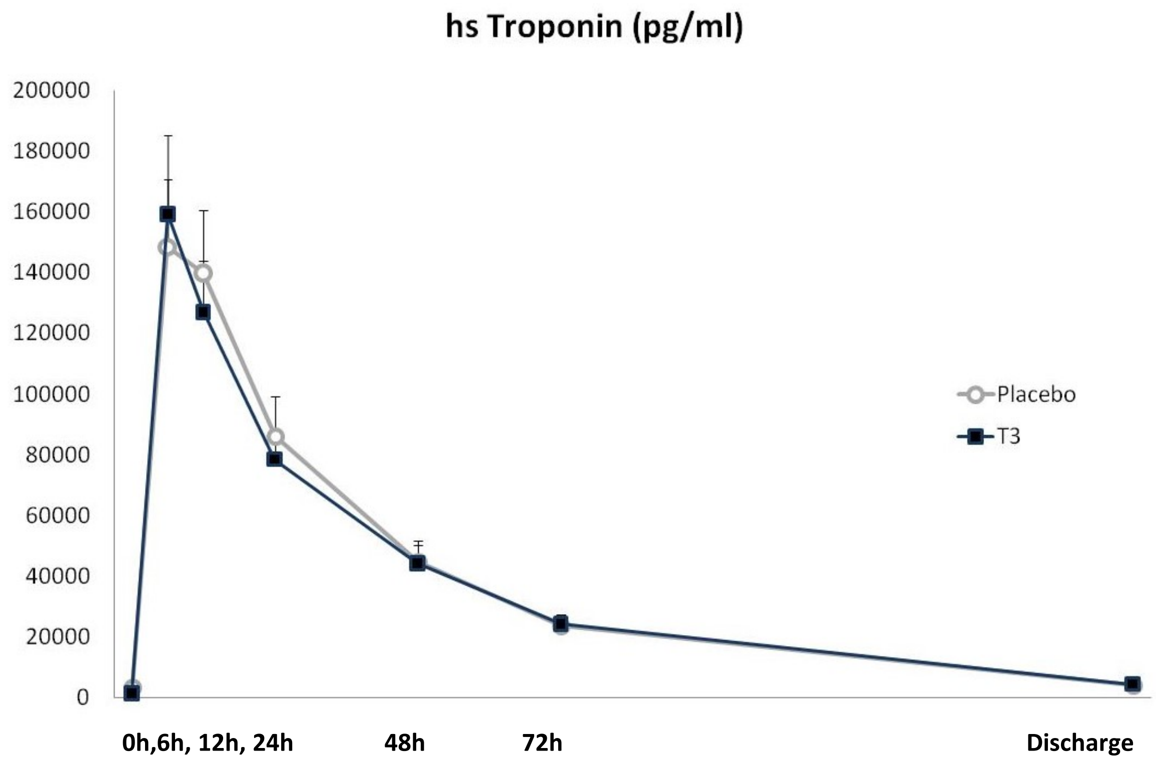
ThyREPAIR : a phase IIa, randomized, double blind, placebo controlled study to translate T3 effects in patients with myocardial infarction





Thyroid. 2022 Jun;32(6):714-724

Myocardial Injury – Troponin Release

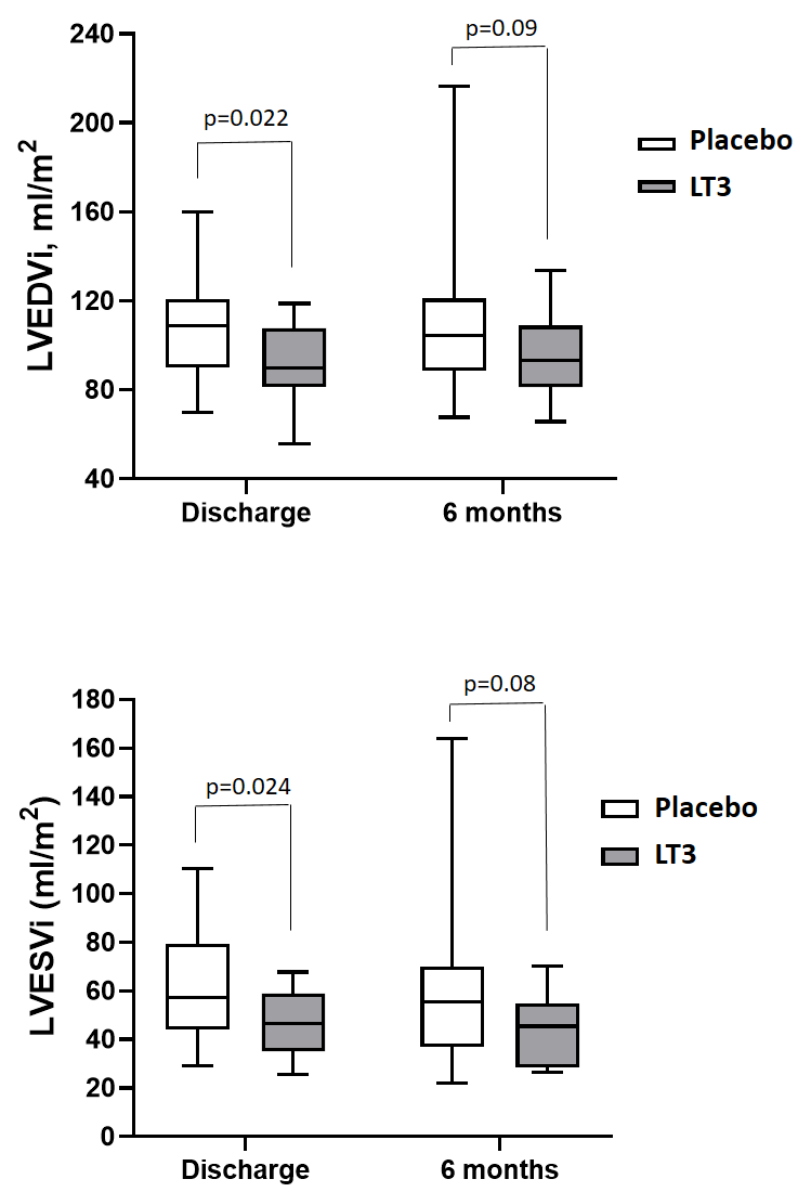


Thyroid. 2022 Jun;32(6):714-724

Results

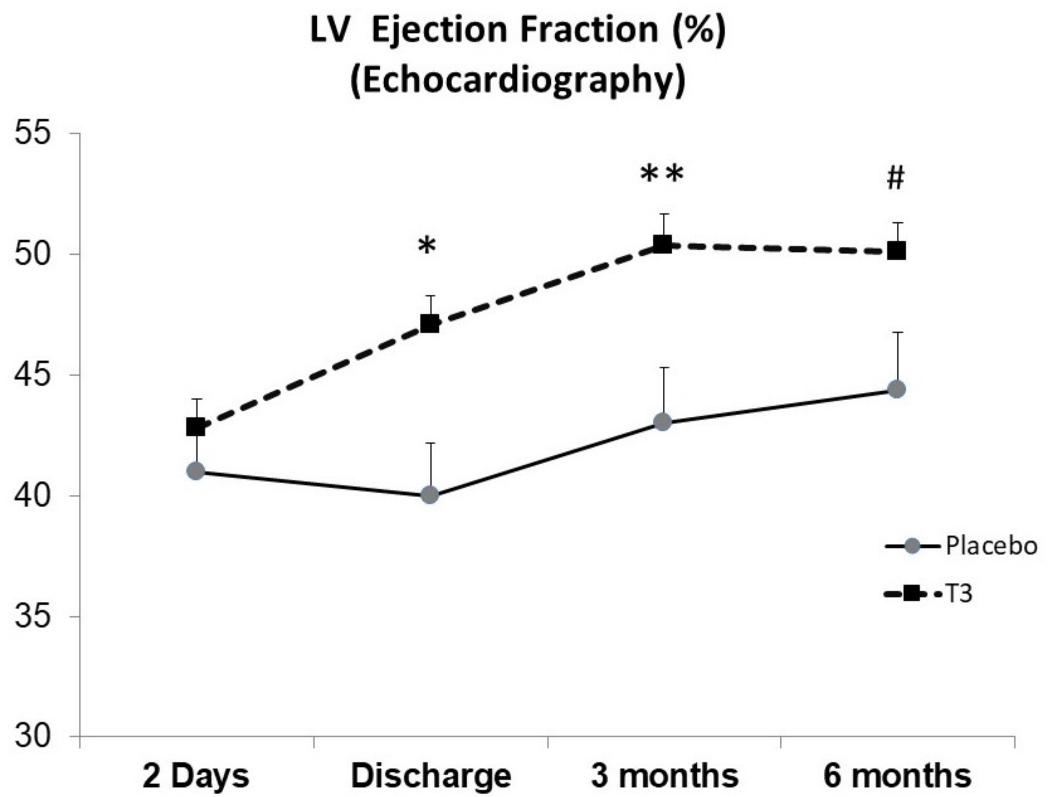
T3 treatment prevents early Cardiac Remodeling after myocardial infarction

Left Ventricular Volumes



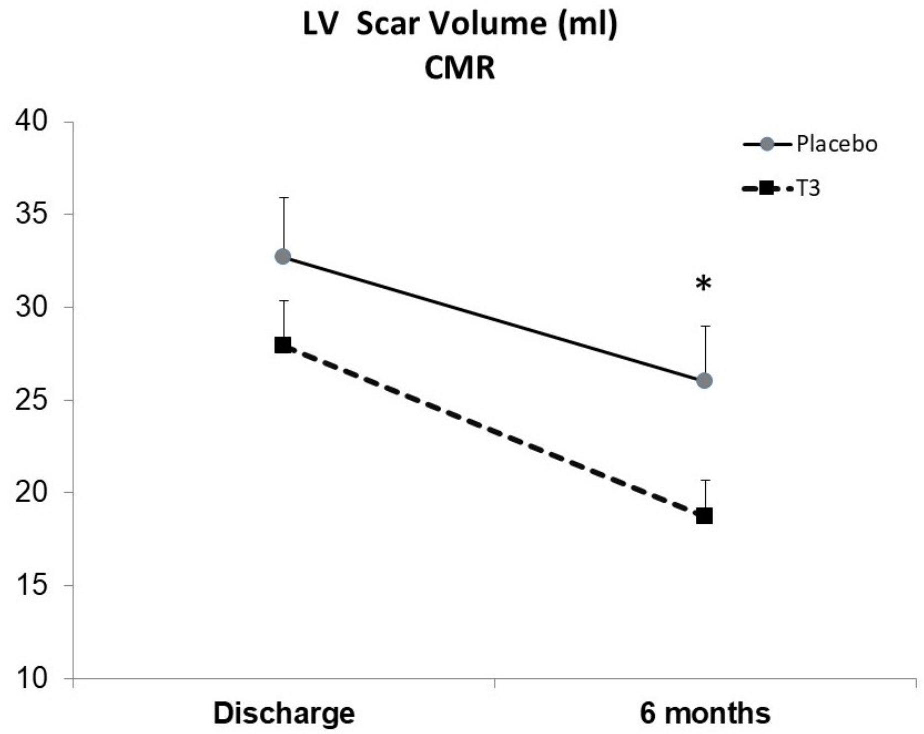
Thyroid. 2022 Jun;32(6):714-724

- T3 treatment improved recovery of cardiac function over time starting early



Indirect evidence of repair/regeneration

- **T3 treatment accelerates healing after myocardial injury (late action)**



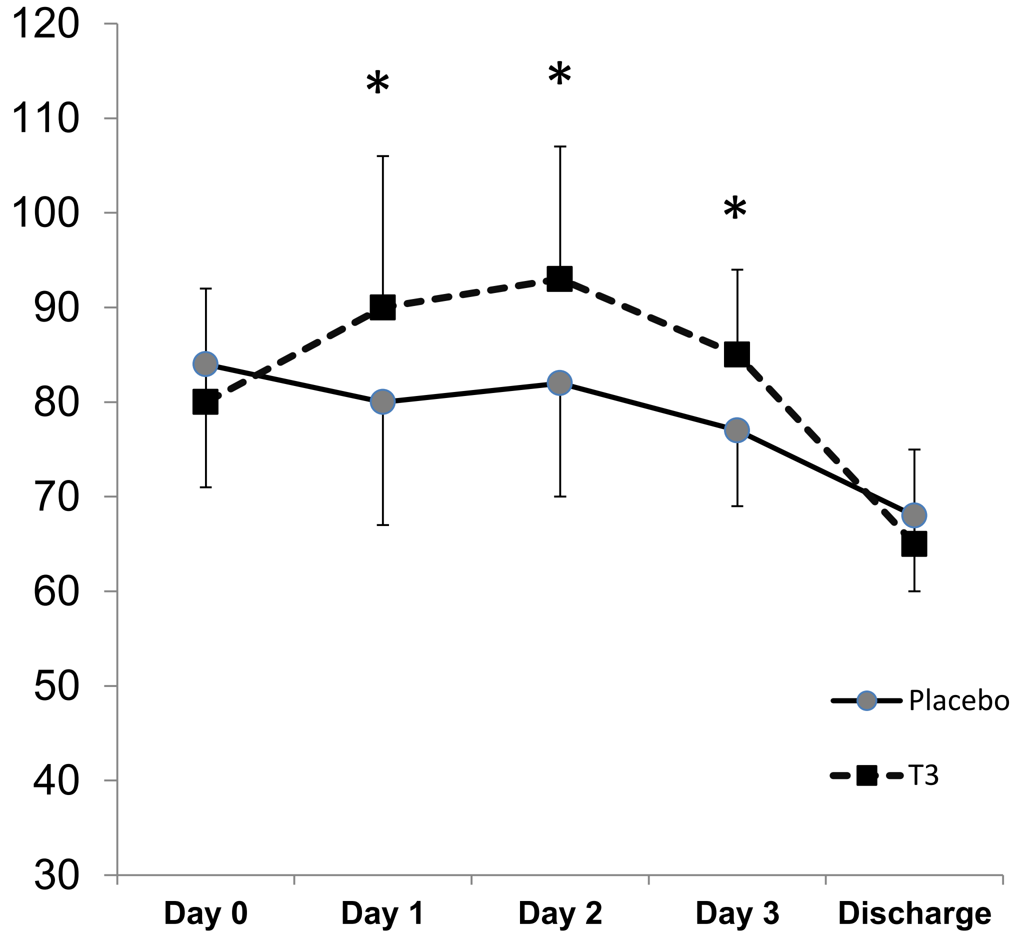
No Serious Adverse Events after T3 treatment

- Safety Issues during hospitalization

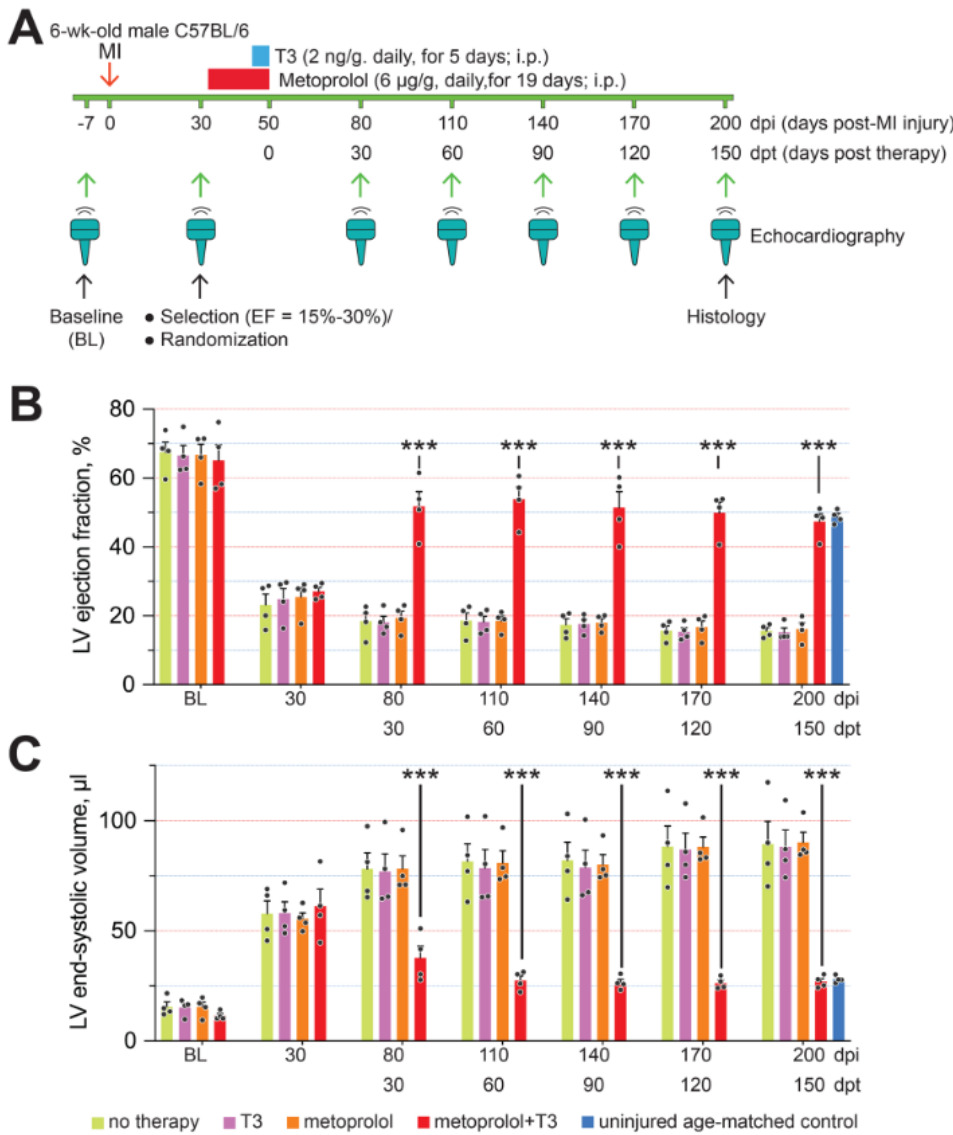
	Placebo (n=22)	T3 (n=26)	
LV thrombus	6/22	4/26	p=0.31
Atrial Fibrillation	1/22	5/26	p=0.13
Minor Hemorrhage	3/22	3/26	p=0.82
Pericarditis	1/22	3/26	p=0.38
High temperature >37.8^{o}C during 48 hours	2/22	8/26	p=0.07
Nervousness	2/22	6/26	p=0.2
Use of inotrops after PCI	4/22	3/26	p=0.51

No Serious Adverse Events after T3 treatment

Heart Rate (beats/min)

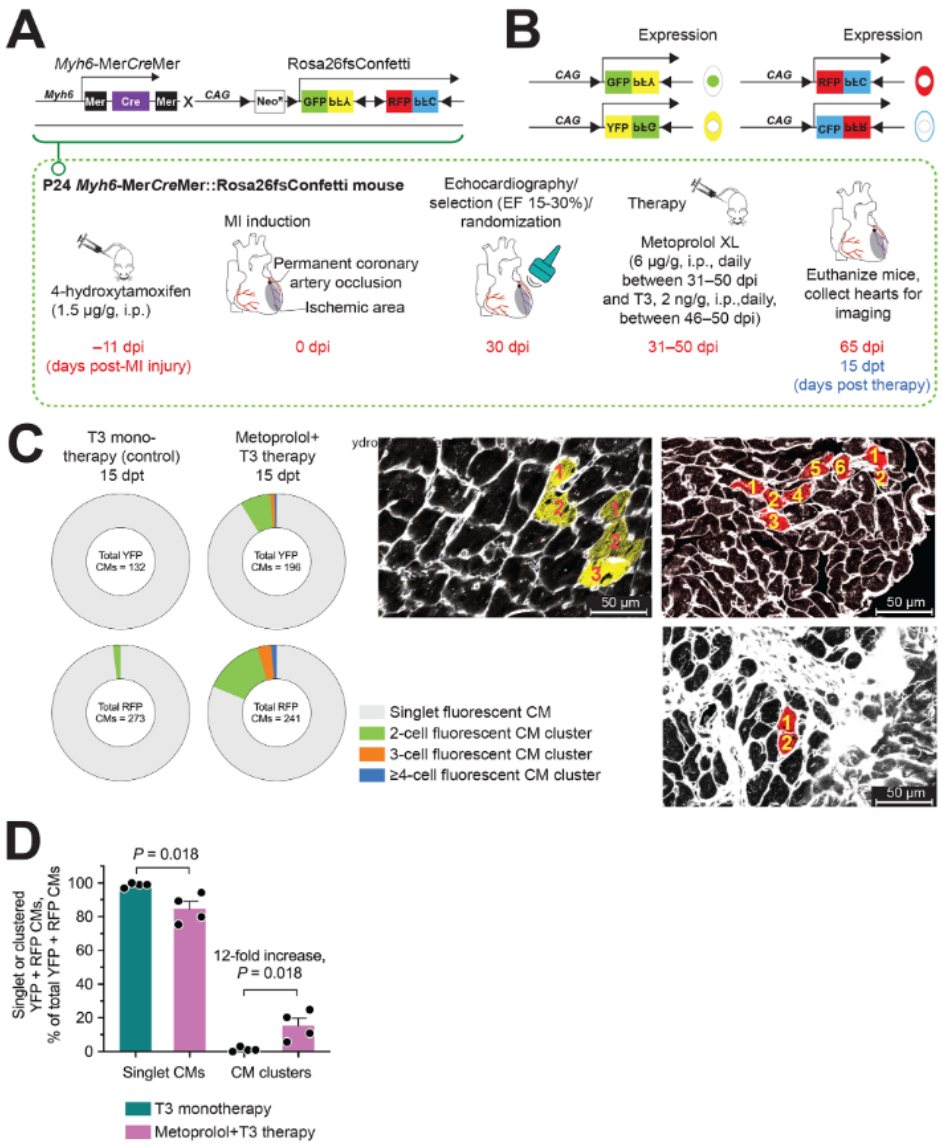


Remuscularization with triiodothyronine and β1 -blocker therapy reverses post-ischemic left ventricular dysfunction and adverse remodeling



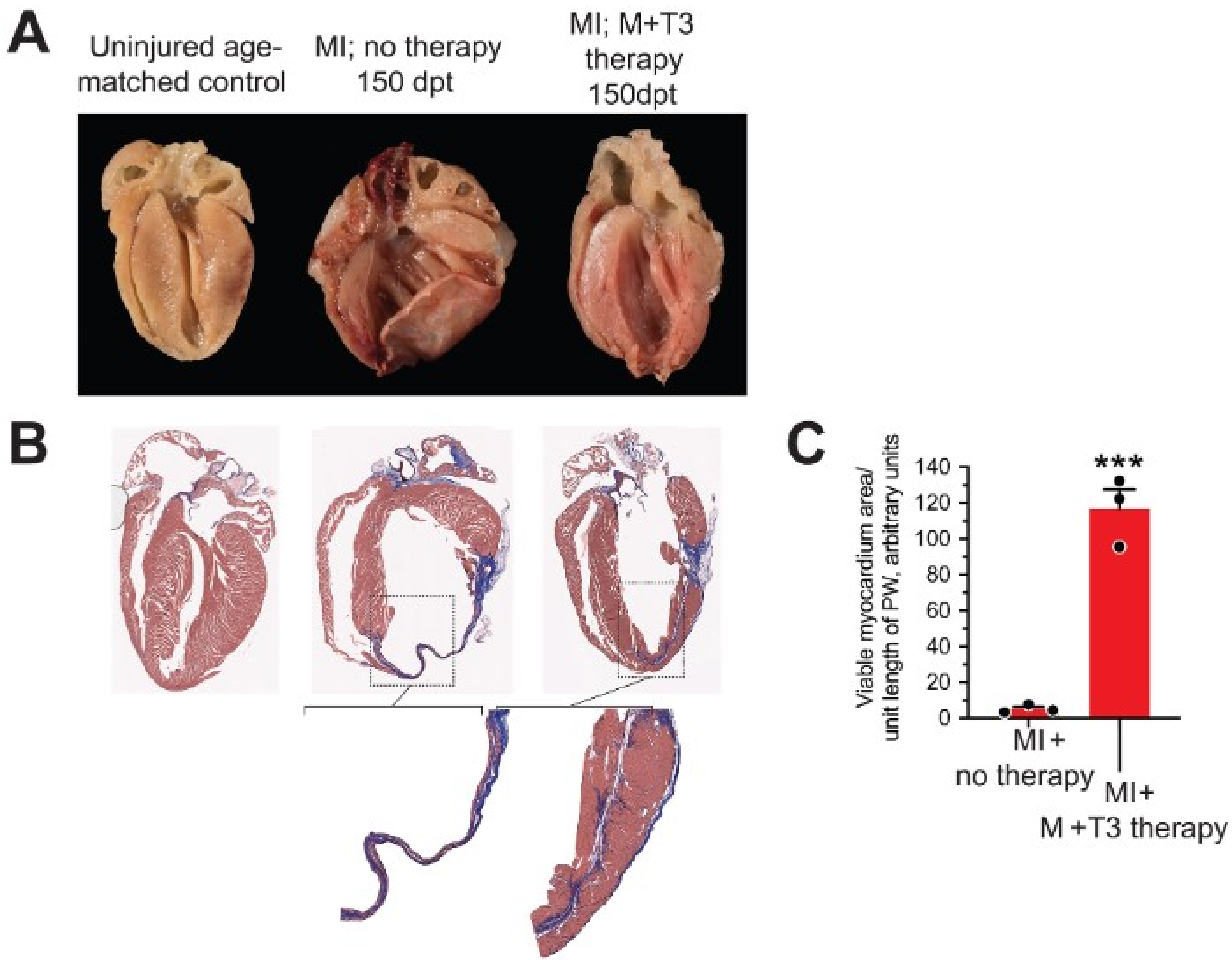
Scientific Reports | (2022) 12:8852

Remuscularization with triiodothyronine and β1 -blocker therapy reverses post-ischemic left ventricular dysfunction and adverse remodeling



Scientific Reports | (2022) 12:8852

Remuscularization with triiodothyronine and β1 -blocker therapy reverses post-ischemic left ventricular dysfunction and adverse remodeling



Conclusions and Future Perspectives

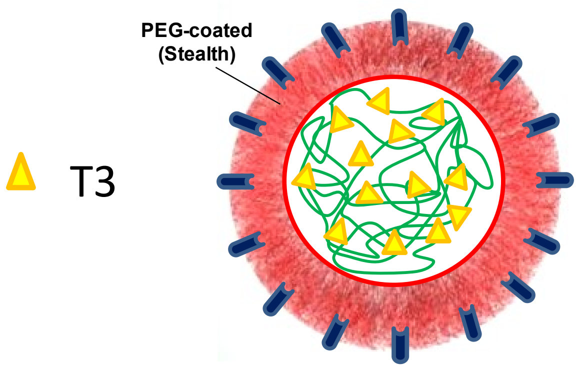
✓Acute, high dose T3 treatment can block the development of cardiac remodeling and heart failure in patients with myocardial infarction

✓TH signalling may have an important role in remuscularization and repair/regeneration of the heart after injury

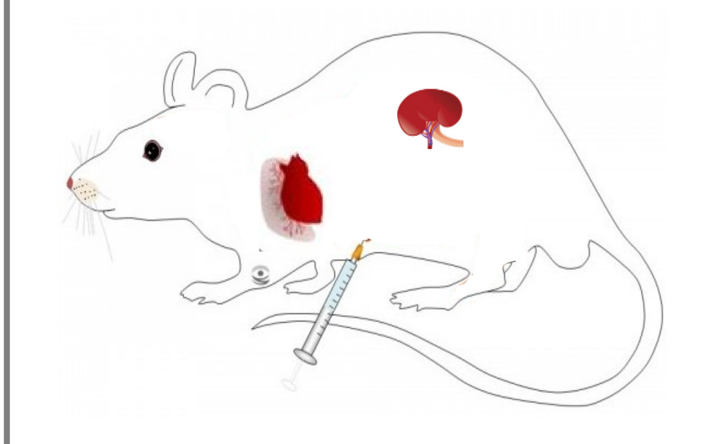
✓ Novel therapeutic approaches: development of stress-specific T3 loaded nanocarriers

EuroNanoMed Research Project

REASON : Regenerating the diabetic heart and kidney by using stress-specific thyroid hormone nanocarriers

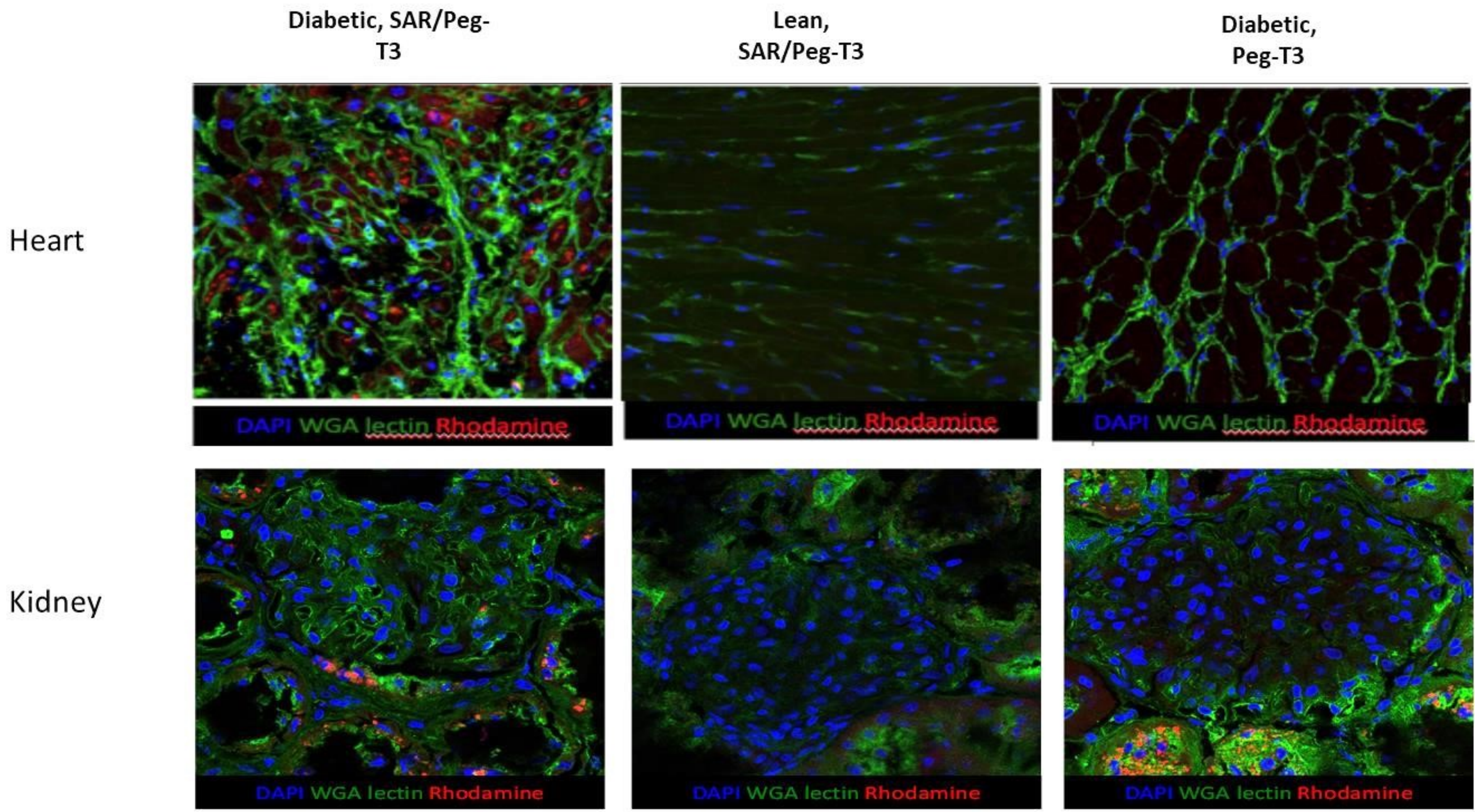


In vivo evaluation in rat model of diabetic nephropathy and cardiomyopathy



Diabetic rat

Diabetic Cardiomyopathy: Evidence of Selective targeting



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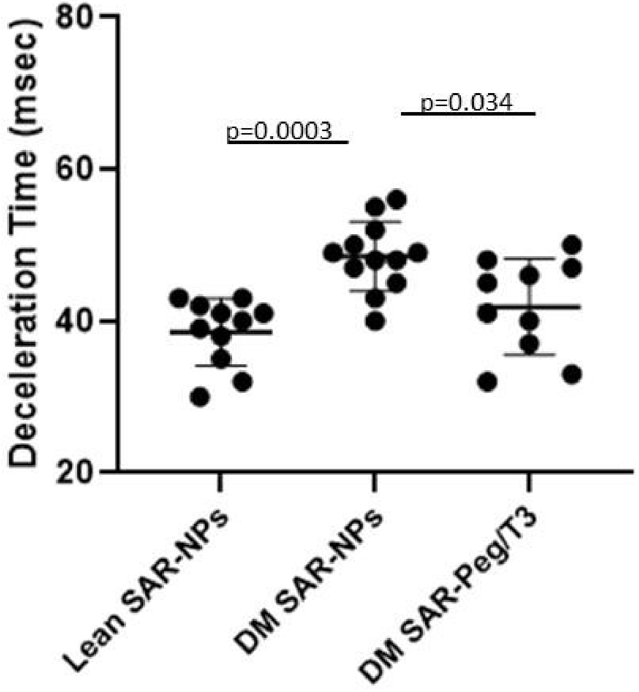
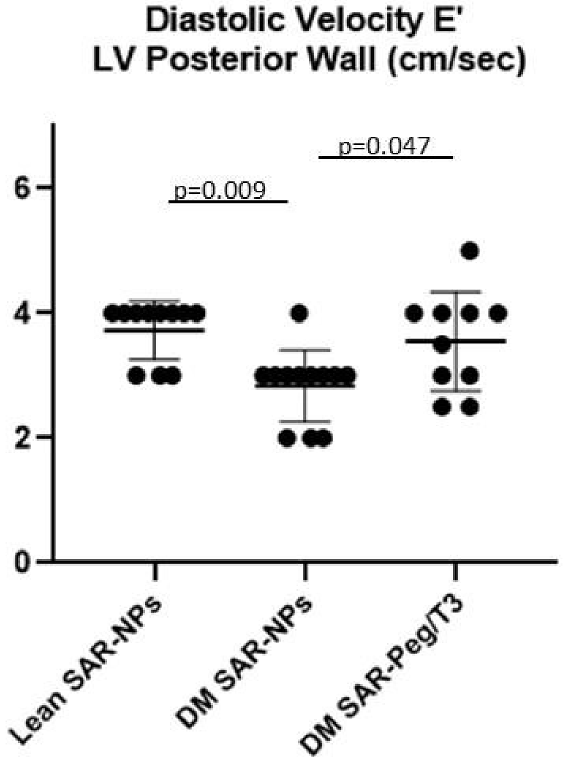
ZDF Diabetic Rats: First Evidence about effectiveness

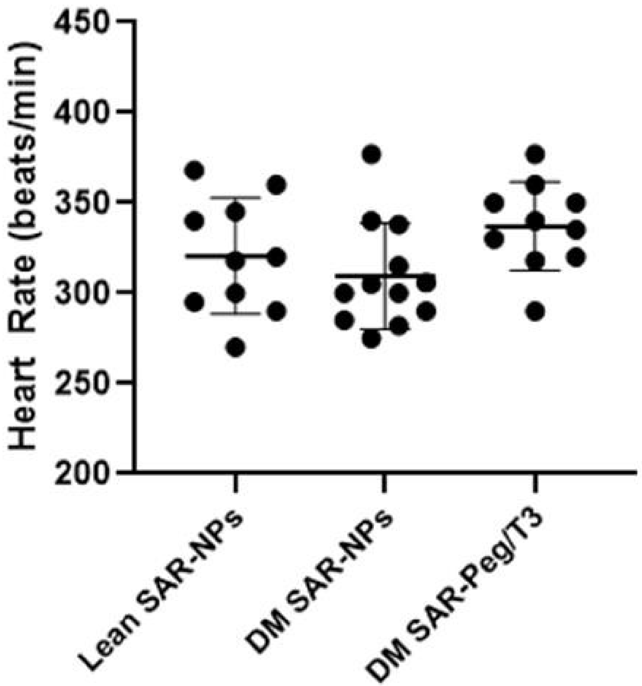
Diastolic Cardiac Function

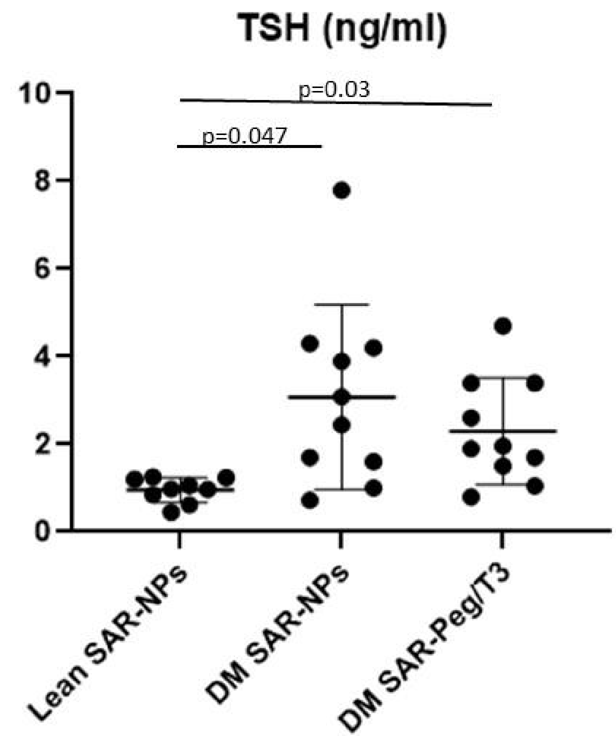




Unpublished data

ZDF Diabetic Rats: Evidence about effectiveness without adverse effects





Unpublished data

Thank you