



Istituto di Fisiologia Clinica  
Consiglio Nazionale delle Ricerche

# ORMONE TIROIDEO E CARDIOPROTEZIONE:

dalla clinica alla ricerca  
sperimentale verso un nuovo  
approccio terapeutico



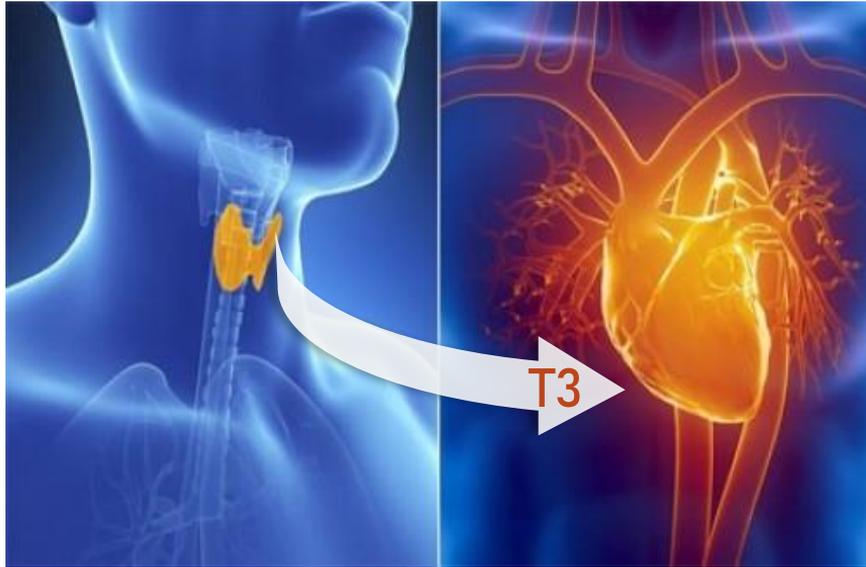
Francesca Forini

# Malattie cardiovascolari: causa #1 di morte nel mondo\*



\* 2015 Heart Disease and Stroke Statistic Update, American Heart Association, Centers for Disease Control and Prevention, the National Institute of Health et al

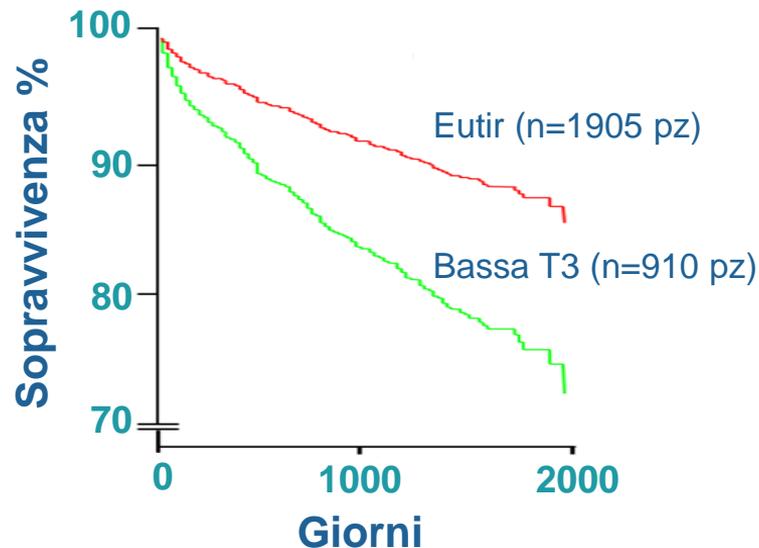
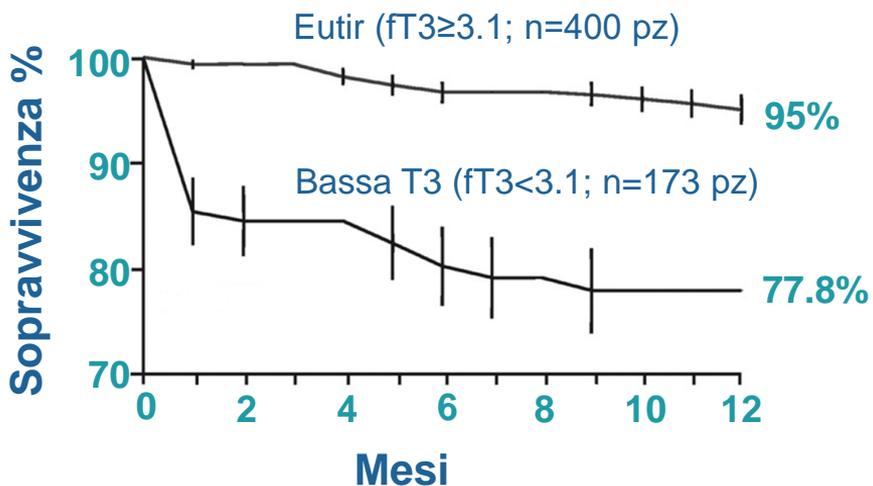
# Asse tiroide-cuore: messaggeri endocrini e omeostasi cardiovascolare



## Effetti funzionali dell' ormone tiroideo biologicamente attivo (T3)

- Contrattilità cardiaca
- Frequenza cardiaca
- Metabolismo cardiaco
- Tono vascolare periferico

# Bassa T3 e mortalità: dati clinici



Low-T3 Syndrome A Strong Prognostic Predictor of Death in Patients With Heart Disease

Iervasi G et al. Circulation 2003

Association Between Increased Mortality and Mild Thyroid Dysfunction in Cardiac Patients

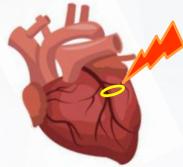
Iervasi G et al. Arch Intern Med 2007

# Modelli Sperimentali

## 1 STUDI PRECLINICI IN VIVO

Ischemia

- acuta
- cronica

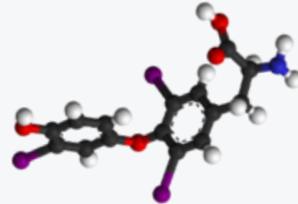


24h/72h



Infusione T3

(3 $\mu$ g/kg/g)

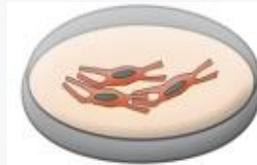


3g/14g/28g

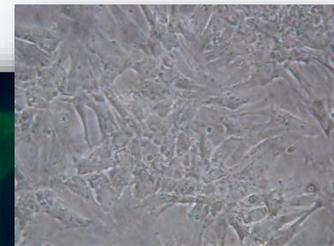
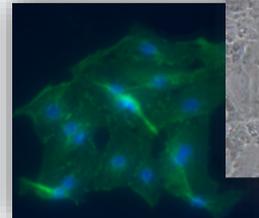


Endpoint

## 2 COLTURE CELLULARI



T3 3nM

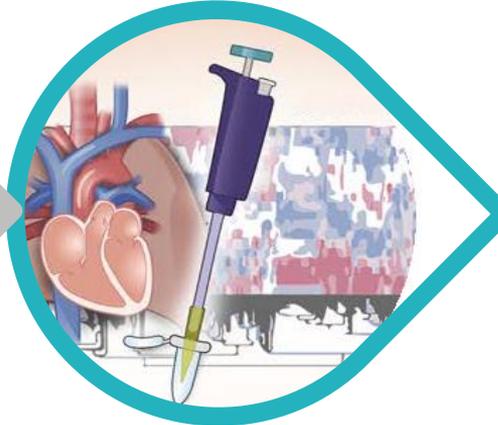


# Metodi di analisi: integrazione di competenze



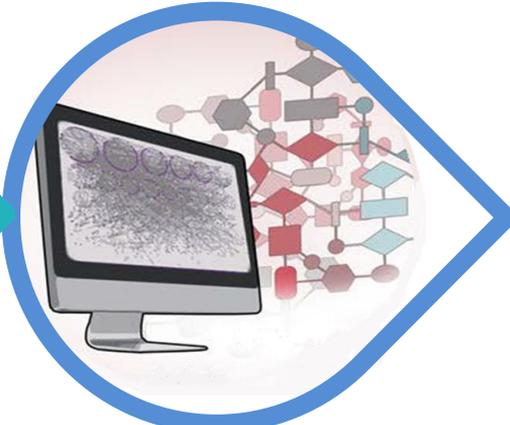
## Studi istologici

- Estensione della lesione
- Morte cellulare
- Fibrosi
- Numero di vasi



## Studi molecolari

- Analisi singoli fattori
- Profili di espressione:  
(mRNA; RNA non codificante;  
proteine)



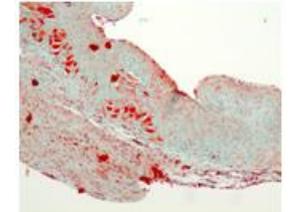
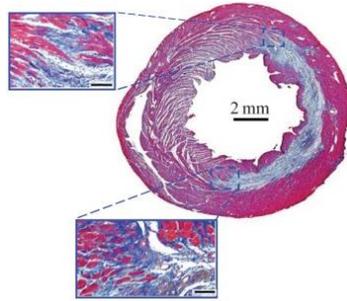
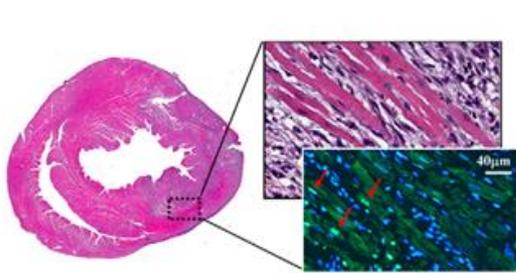
## Procedure computazionali

- Integrazione di dati
- Identificazione circuiti regolatori

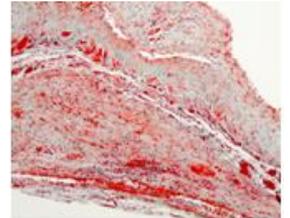
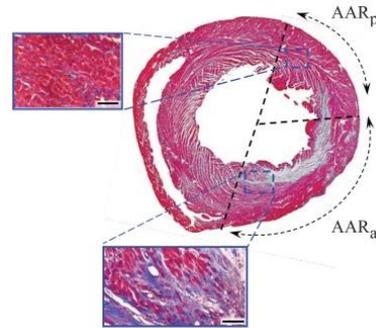
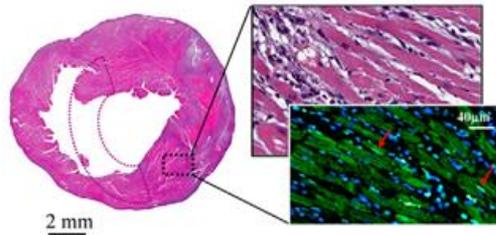
# Effetto T3: riparazione della lesione



-T3



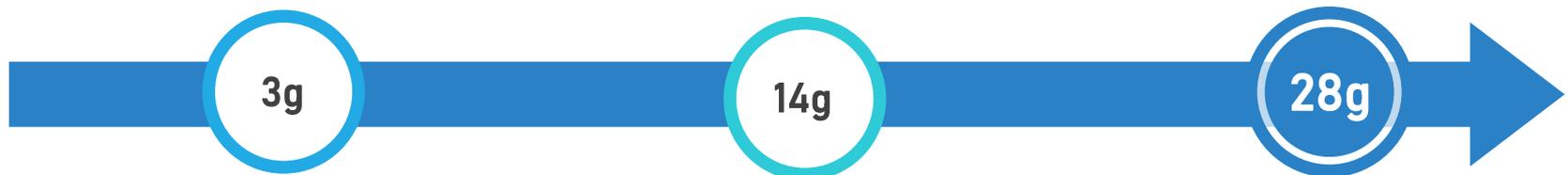
+T3



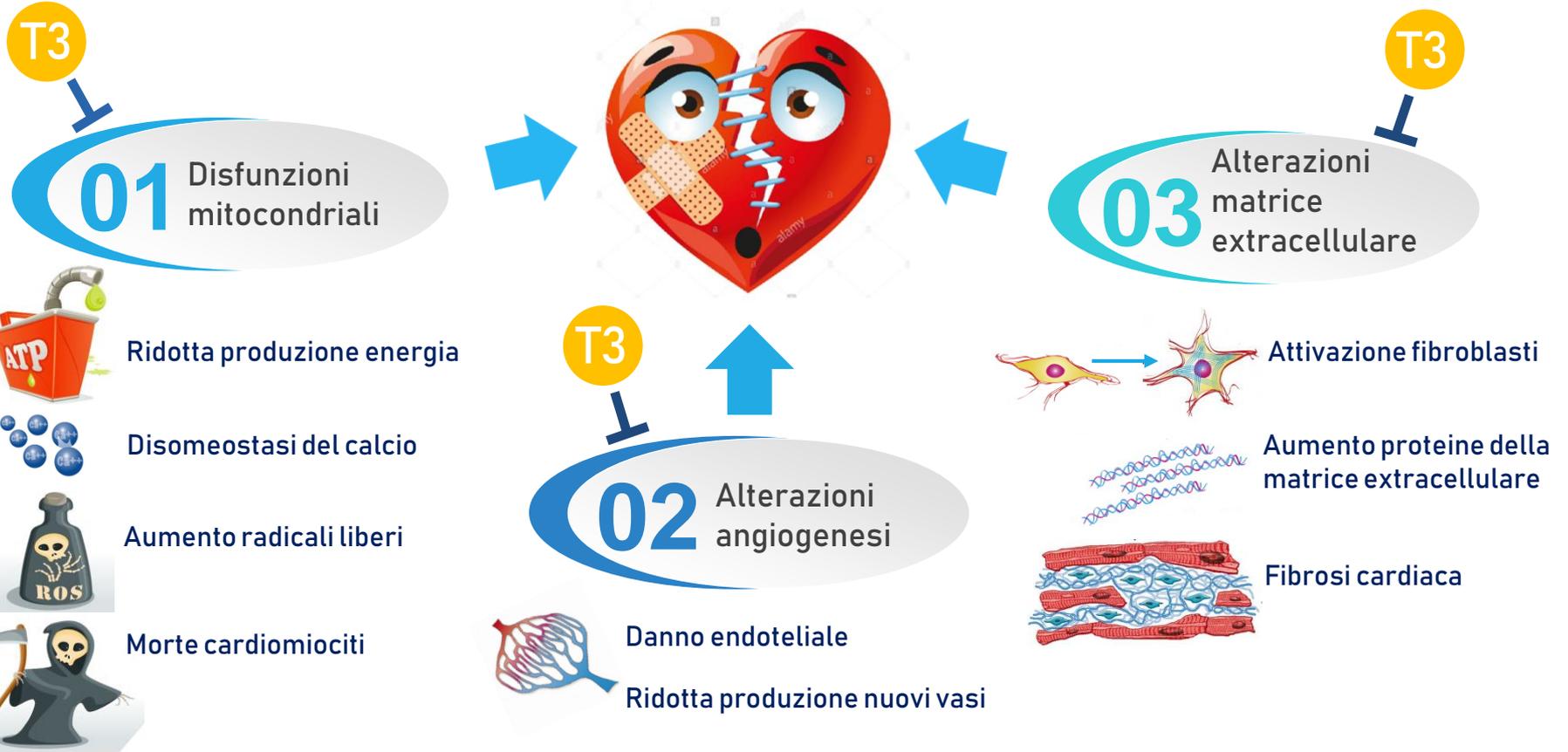
3g

14g

28g



# Effetto T3: processi coinvolti



# Effetto T3: circuiti regolatori miRNA/geni



## miRNA

## Geni target antimodulati

## Azione cardioprotettiva

↓ mir-222  
↓ mir-31a  
↓ mir-155



Pgc1 $\alpha$ , Mfn2, Cpt2  
Sod1, Sod2  
Bnip3



↑ Produzione energia  
↑ Difese antiossidanti  
↑ Controllo di qualità dei mitocondri

↑ mir-29  
↑ mir-208a  
↑ mir-499  
↑ mir-133  
↑ mir-30  
↑ mir-338



Tgfb1, Tgfbr, Ctgf, Col, Mmp  
P53, Bax, Bak, Pmaip, Bid  
Itgb1, Itgb5  
Jun, Sp1, Stat,  
Faslg, Cxcr4



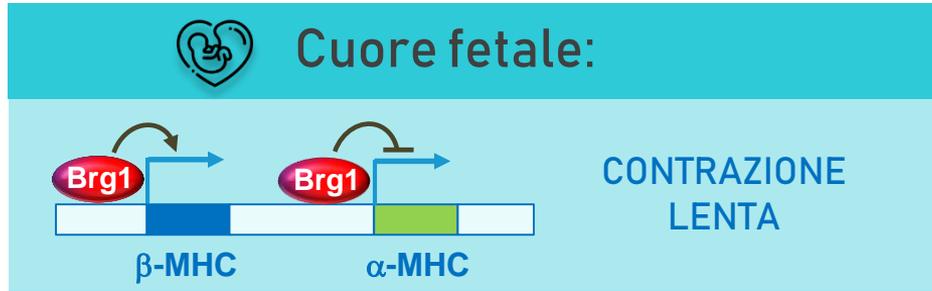
↓ Fibrosi  
↑ Sopravvivenza cardiomiociti  
↓ Adesione cellulare  
↑ Morfogenesi vasale  
↓ Processi infiammatori

The Stimulative Effect of T3 and T4 on Human Myocardial Endothelial Cell Proliferation, Migration and Angiogenesis

Early and Short-term Triiodothyronine Supplementation Prevents Adverse Postischemic Cardiac Remodeling: Role of Transforming Growth Factor- $\beta$ 1 and Antifibrotic miRNA Signaling

Integrative analysis of differentially expressed genes and miRNAs predicts complex T3-mediated protective circuits in a rat model of cardiac ischemia reperfusion

# In corso: T3 e regolazione epigenetica delle isoforme della miosina



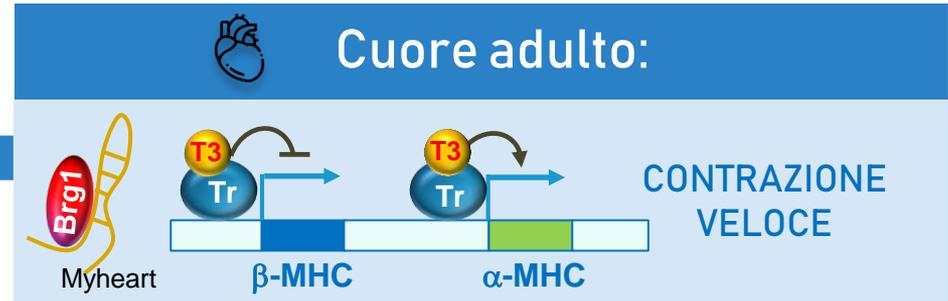
Differenziamento:

- Myheart sequestra Brg1
- Derepressione  $\alpha$ -miosina
- Riduzione  $\beta$ -miosina

~~Stress cardiaco:~~

- ~~• Aumento livelli di Brg1~~
- ~~• Riduzione livelli MyHeart~~
- ~~• Derepressione  $\beta$ -miosina~~
- ~~• Riduzione  $\alpha$ -miosina~~

T3



# Conclusioni

- 1** Dimostrazione nesso causale fra bassa T3 e danno cardiaco
- 2** Identificazione di un nuovi circuiti cardioprotettivi T3-dipendenti
- 3** Definizione di un nuovo protocollo di trattamento sicuro e traslabile

# Partecipanti allo studio



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# Grazie

