

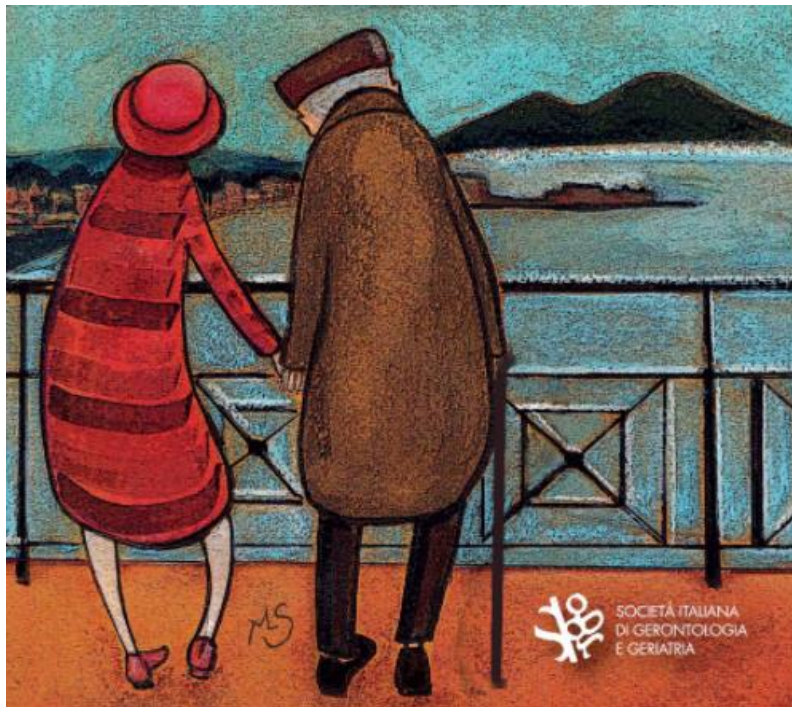


UNIVERSITÀ DEGLI  
STUDI DI NAPOLI  
FEDERICO II



## **“I CROSS-TALK RECETTORIALI NELLA REGOLAZIONE DELLA FUNZIONE MIOCARDICA”**

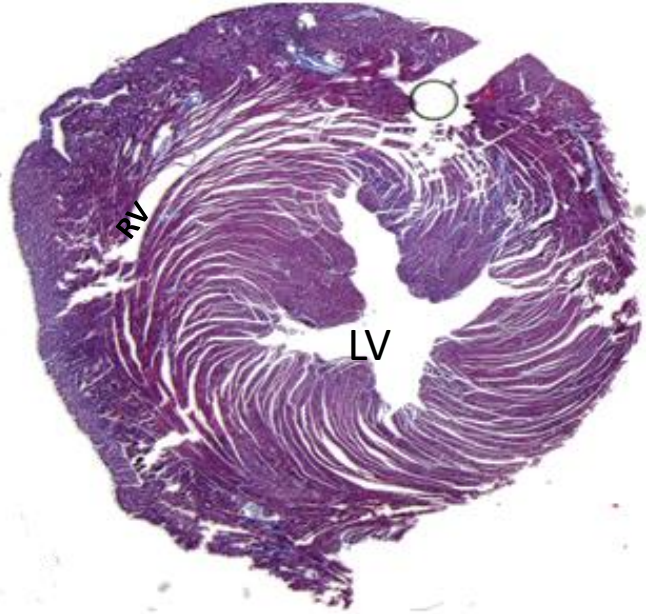
***Nuove (e vecchie) strategie terapeutiche nell'insufficienza cardiaca***



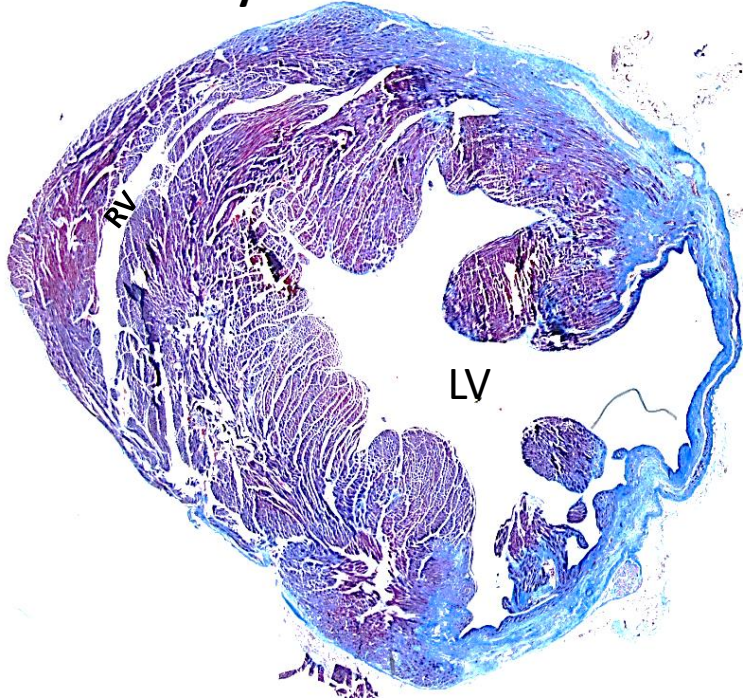
**Alessandro Cannavo, PhD**

Research Fellow  
Dipartimento di Scienze Mediche Traslazionali  
Universita' degli studi di Napoli "Federico II"

Healthy



Myocardial Infarction



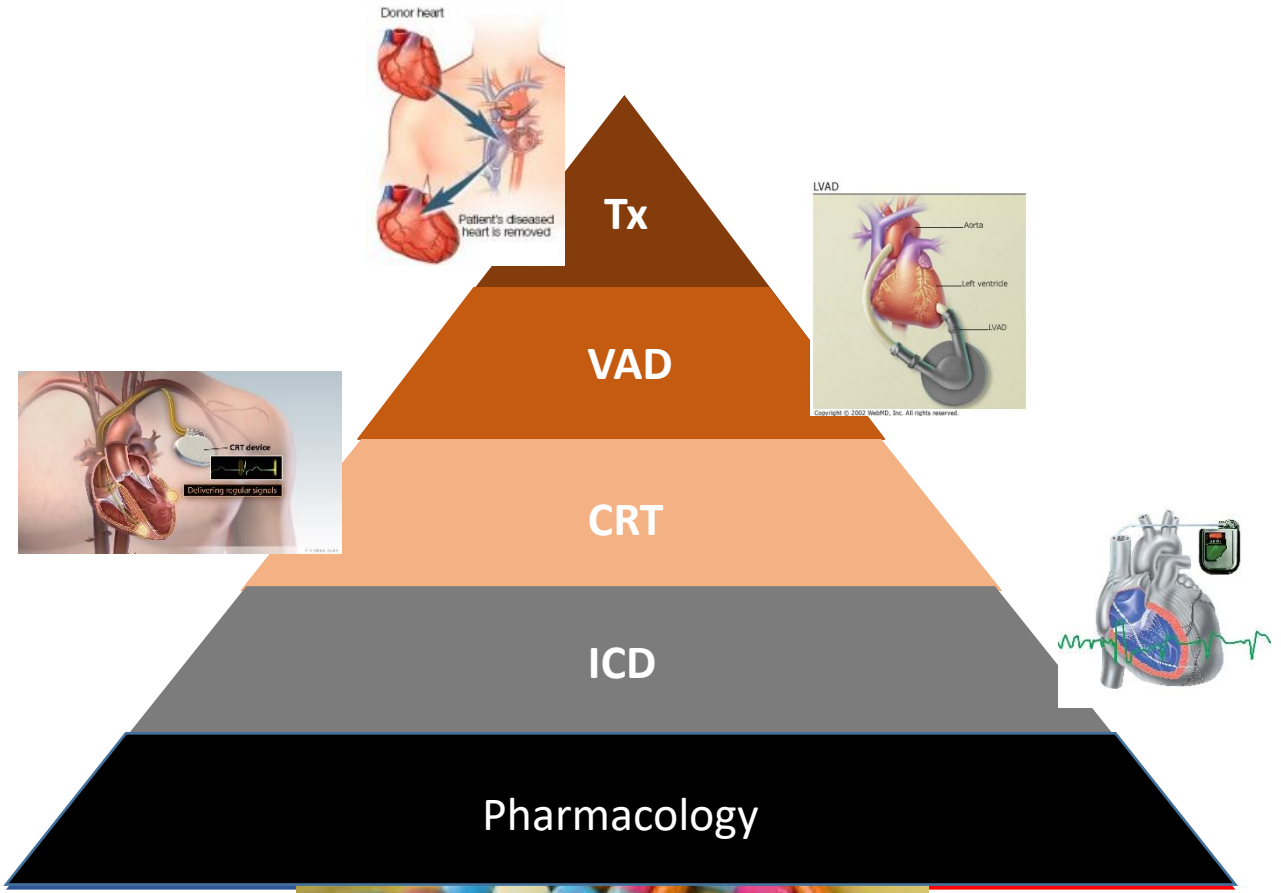
# Heart Failure

- Heart failure: one of the leading causes of morbidity and mortality worldwide, with a myocardial infarction (MI) as the most common etiology.
- “Heart Failure is a complex syndrome that results from any structural and functional impairment of ventricular filling or ejection of blood.”

# The building blocks of HF-Therapy

**Digoxin**

**CABG**



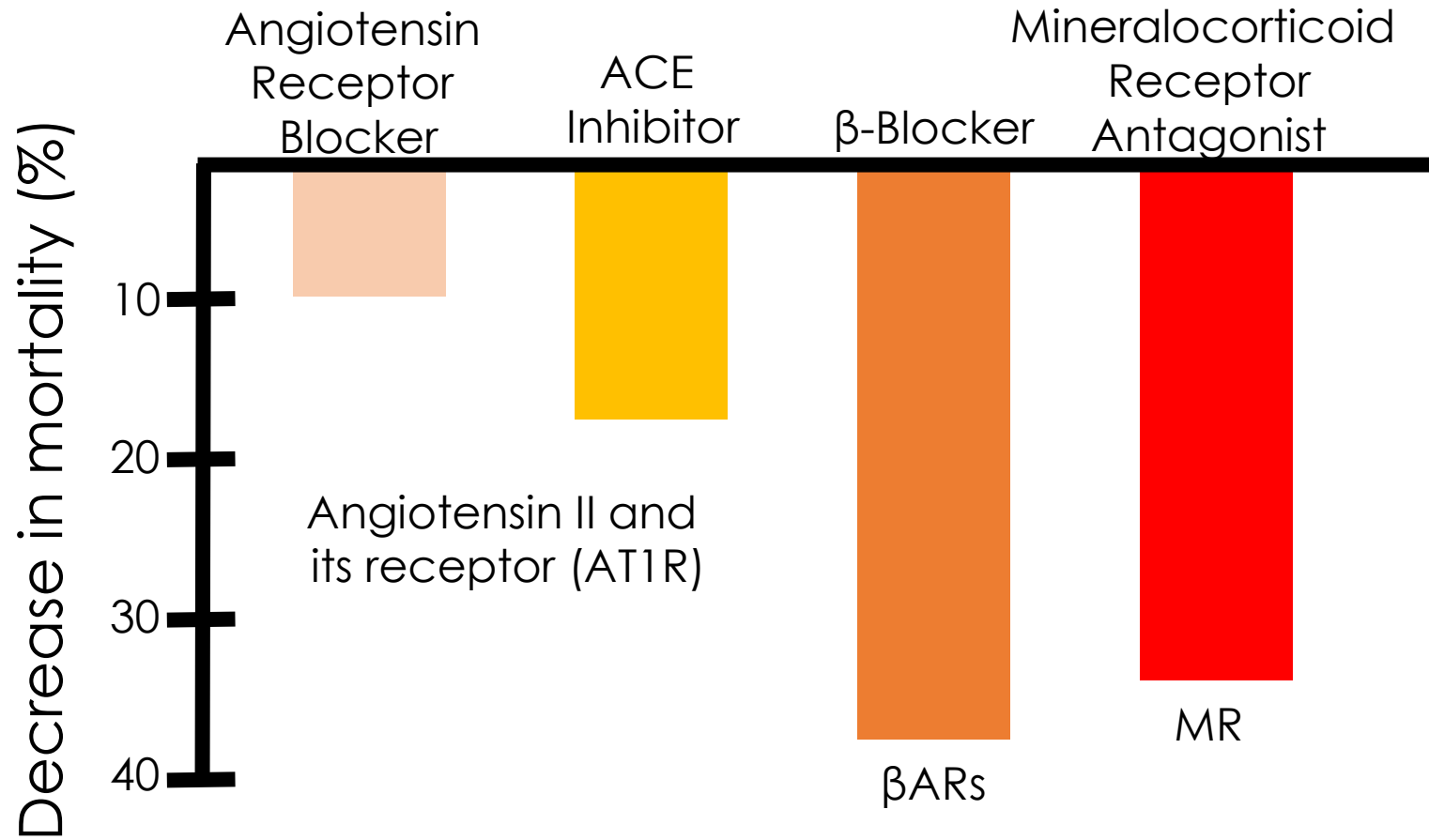
**Ivabradine**

**H-ISDN**



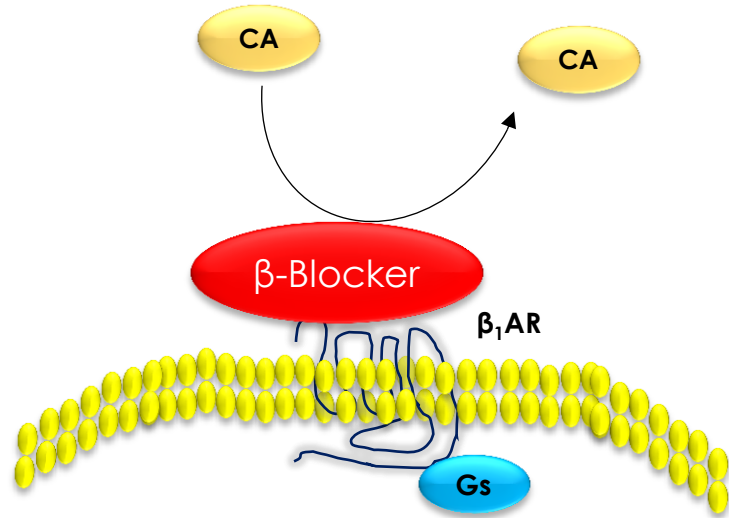
Ponikowski et al. Eur Heart J. 2016

# Pharmacological Therapy



Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

# $\beta$ -blockers in cardiovascular disease...

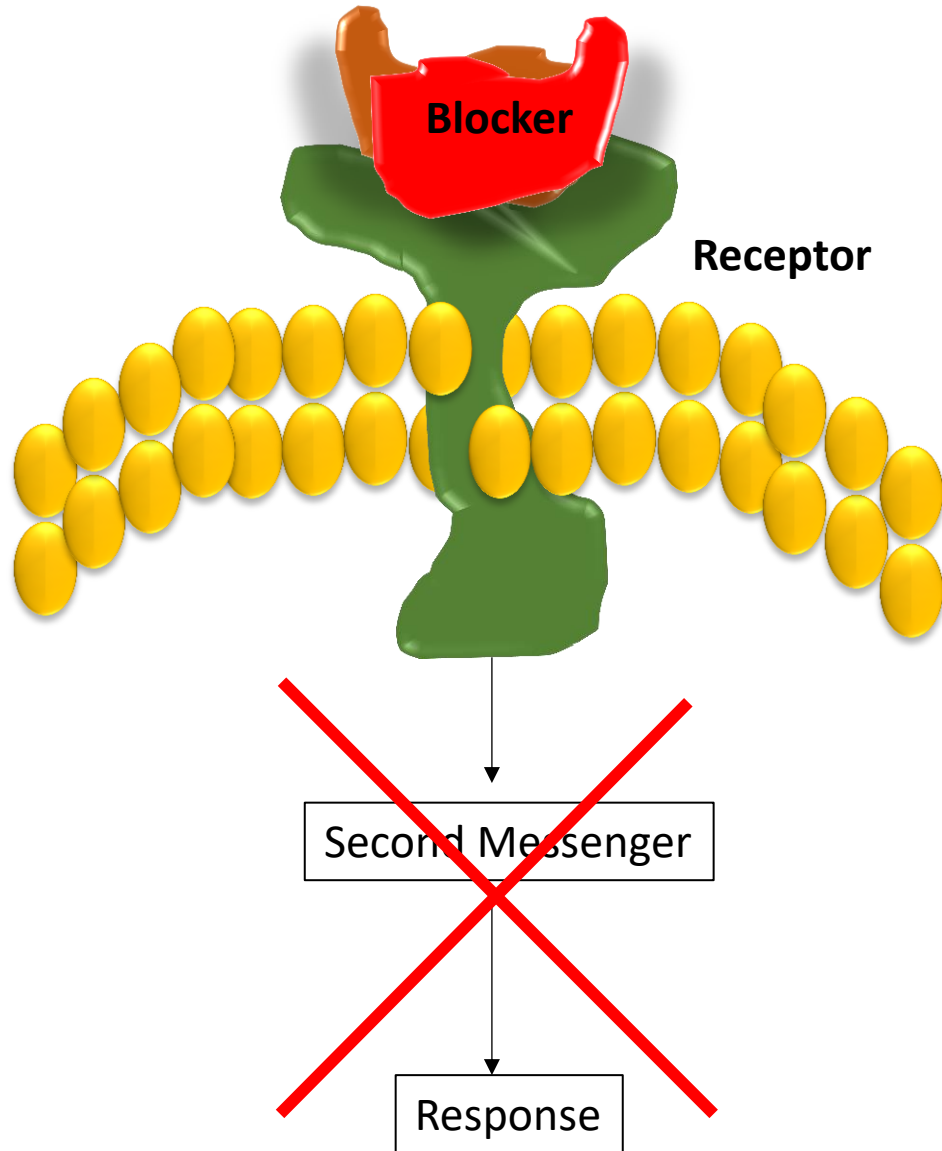


- ...prevent cardiac adverse remodeling
- ...blunt cardiomyocytes apoptosis
- ...reduce risk of fatal arrhythmias
- ...slow heart rate
- ...induce vasodilation

$\beta$ -blocker therapy  
is not suitable to all patients

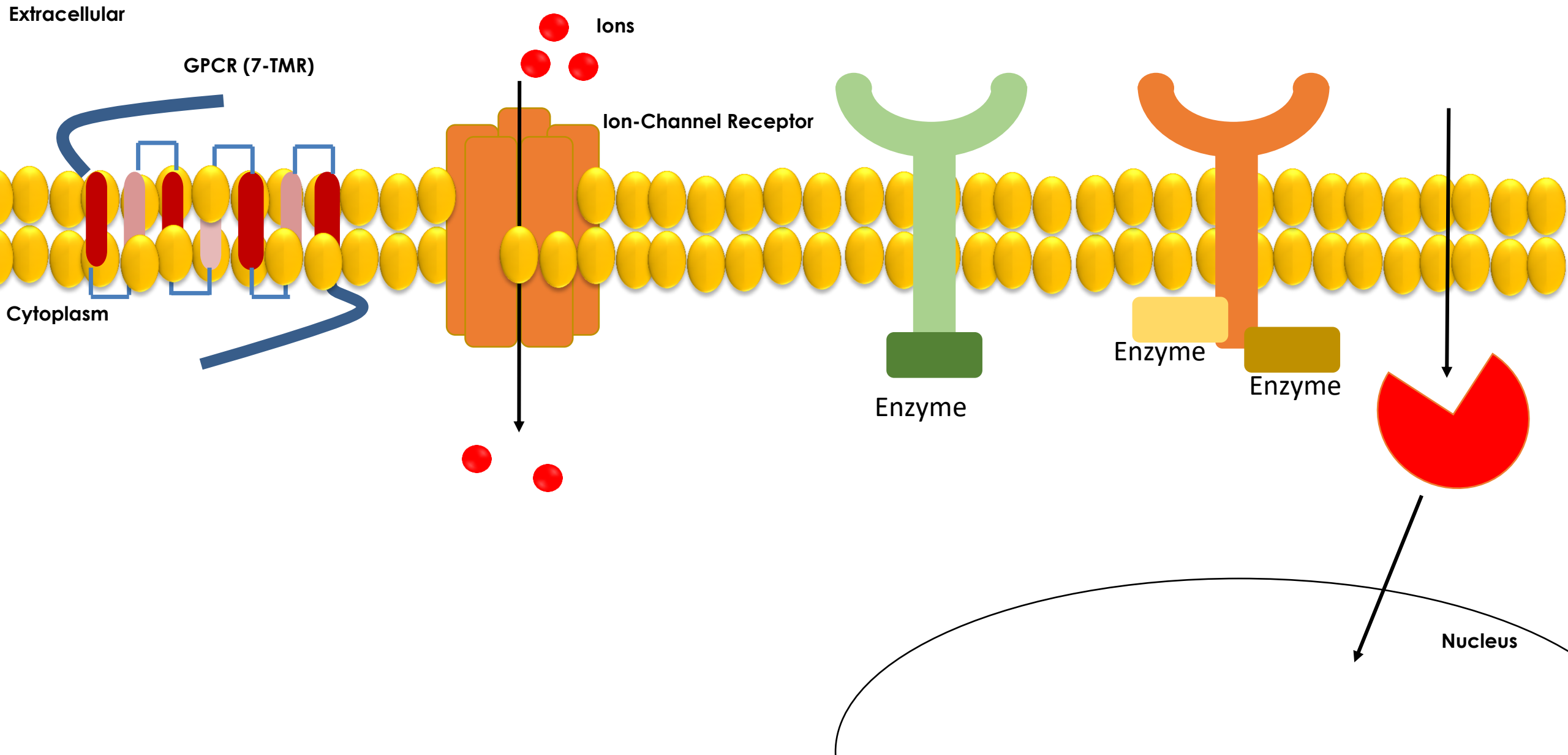
**Additional mechanisms?**

# Receptor and Ligand

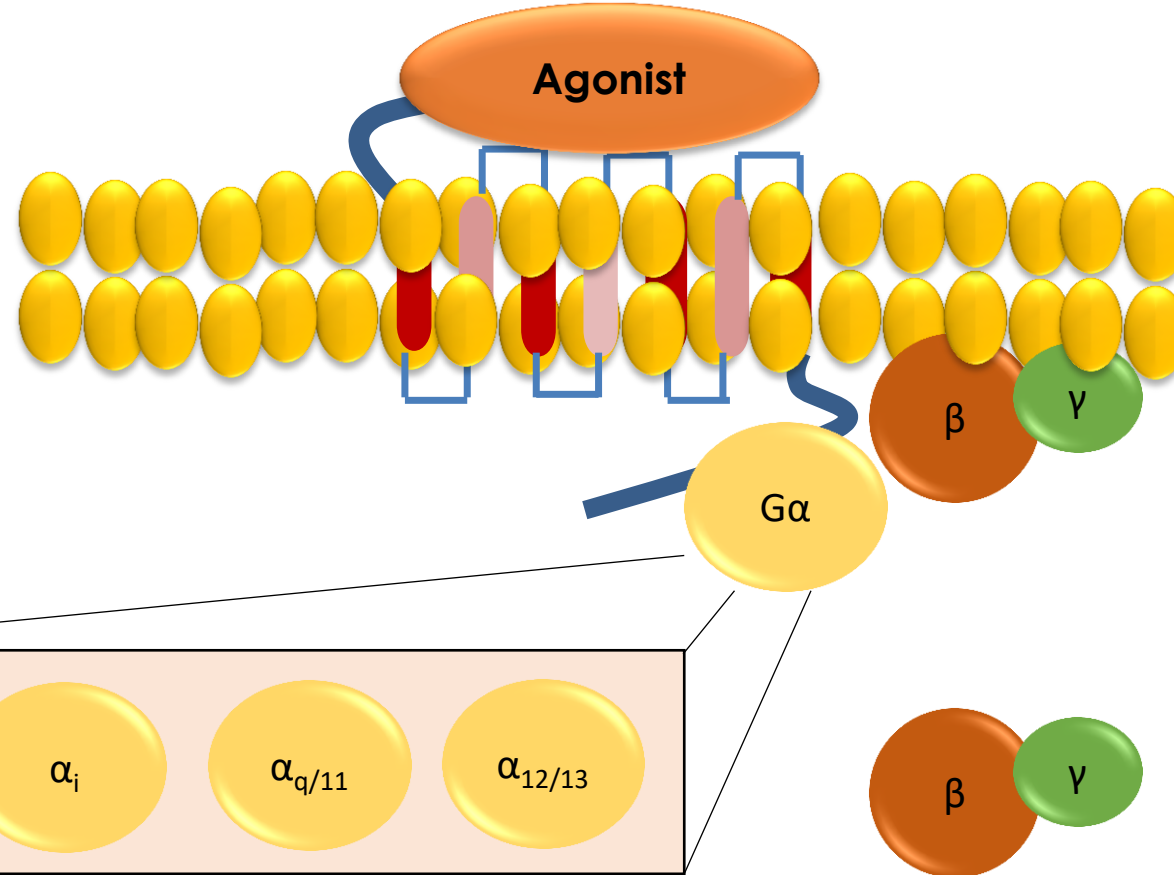


- Ligand - Molecule that bind the receptor activating a specific intracellular response**
- Blocker/Antagonist – Molecule that bind the receptor but not induce its activation**

# Types of receptors



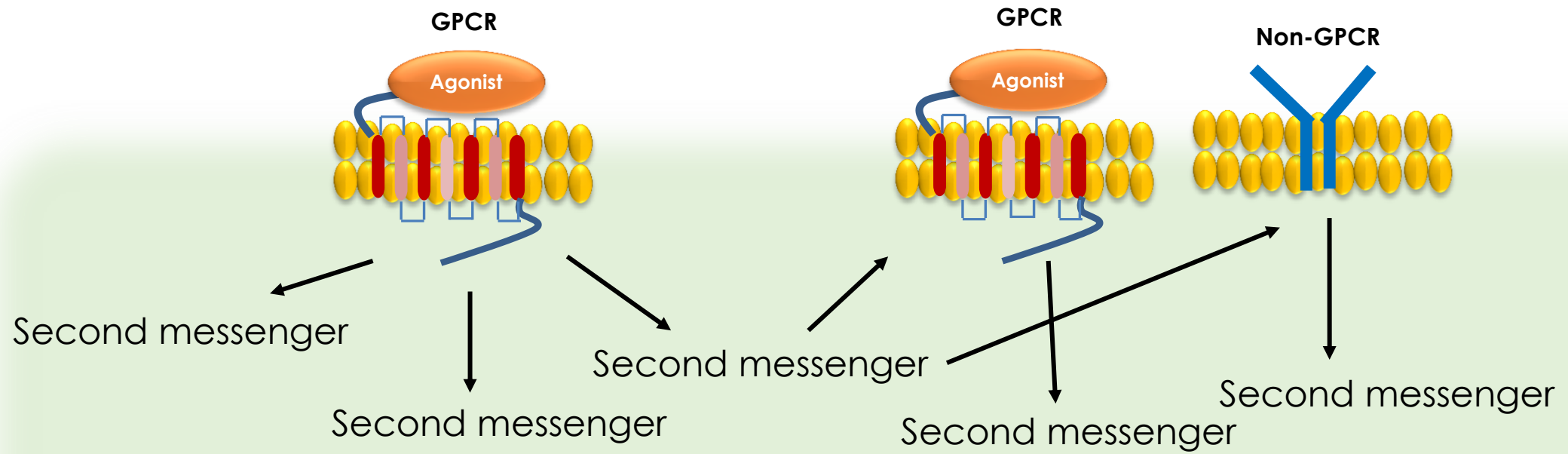
# G-protein coupled receptor (GPCR)



- $\alpha$ - and  $\beta$ -adrenergic receptors (ARs)
- $M_2$ - and  $M_3$ -muscarinic acetylcholine receptors (mAChRs)
- Angiotensin II (Ang II) type 1 receptors ( $AT_1$ Rs)

Multiple Signaling Pathways

# Receptor Cross Talk



# Cross-talk between $\alpha$ - and $\beta$ -adrenergic receptors

J Mol Cell Cardiol 30, 1827-1839 (1998)  
Article No. mc980746

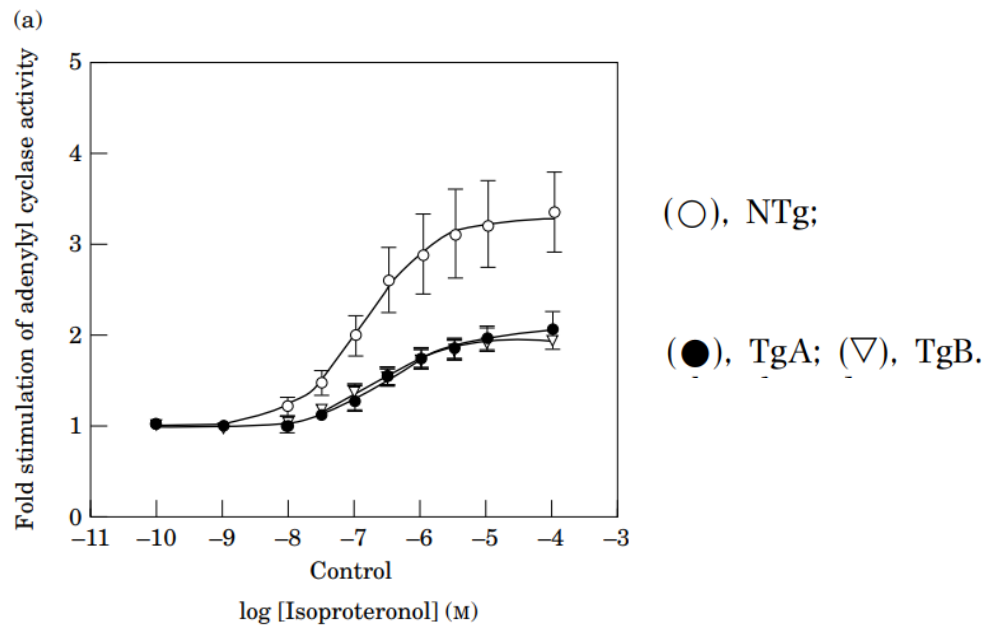


## Cardiac-specific Overexpression of $\alpha_{1B}$ AR Regulates $\beta$ AR Activity Via Molecular Crosstalk

Isabelle Lemire<sup>1</sup>, Bruce G. Allen<sup>1,2</sup>, Hansjörg Rindt<sup>1,2</sup> and Terence E. Hebert<sup>1,3\*</sup>

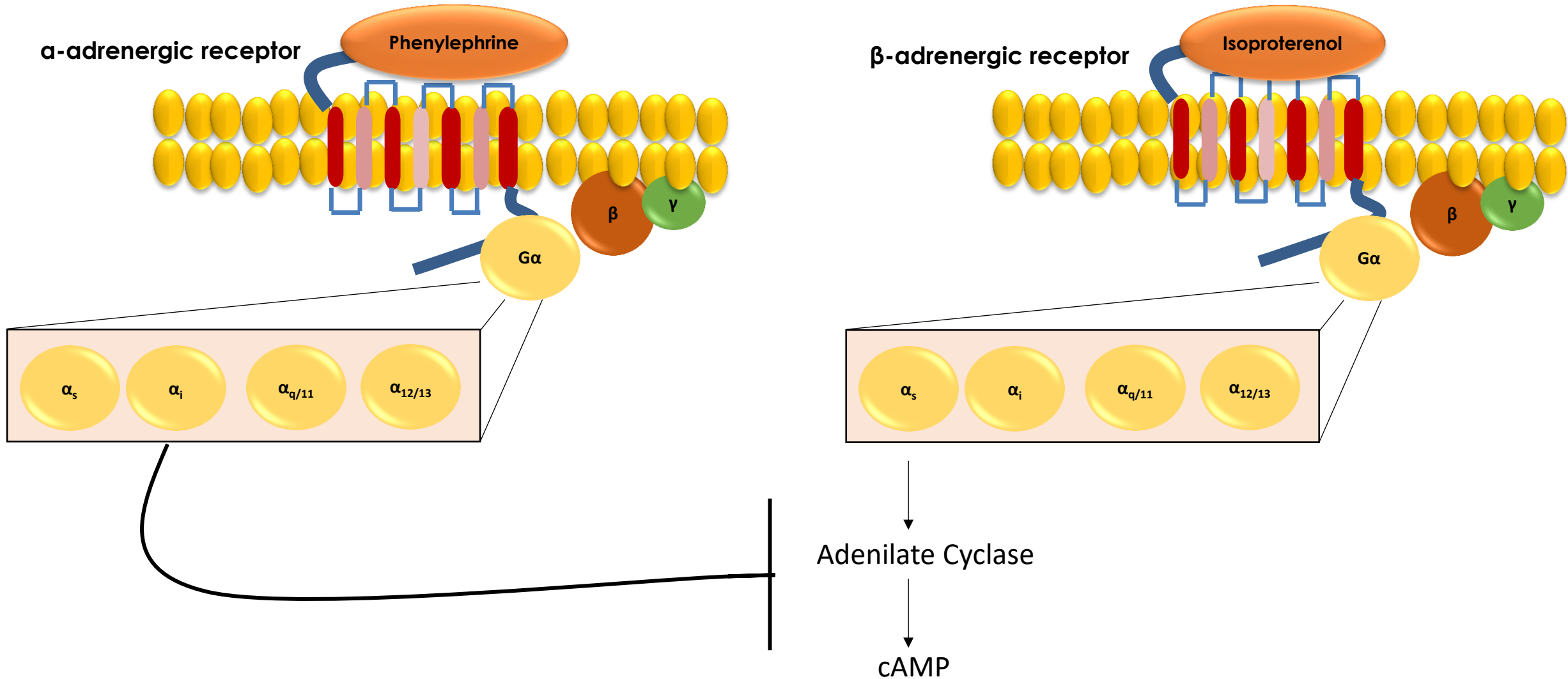


↑  $\alpha_{1B}$ AR




*Isoproterenol-mediated fold stimulation of adenylyl cyclase activity of both transgenic mouse lines was decreased significantly*

# $\alpha$ -adrenoceptor-mediated inhibition of cellular cAMP accumulation

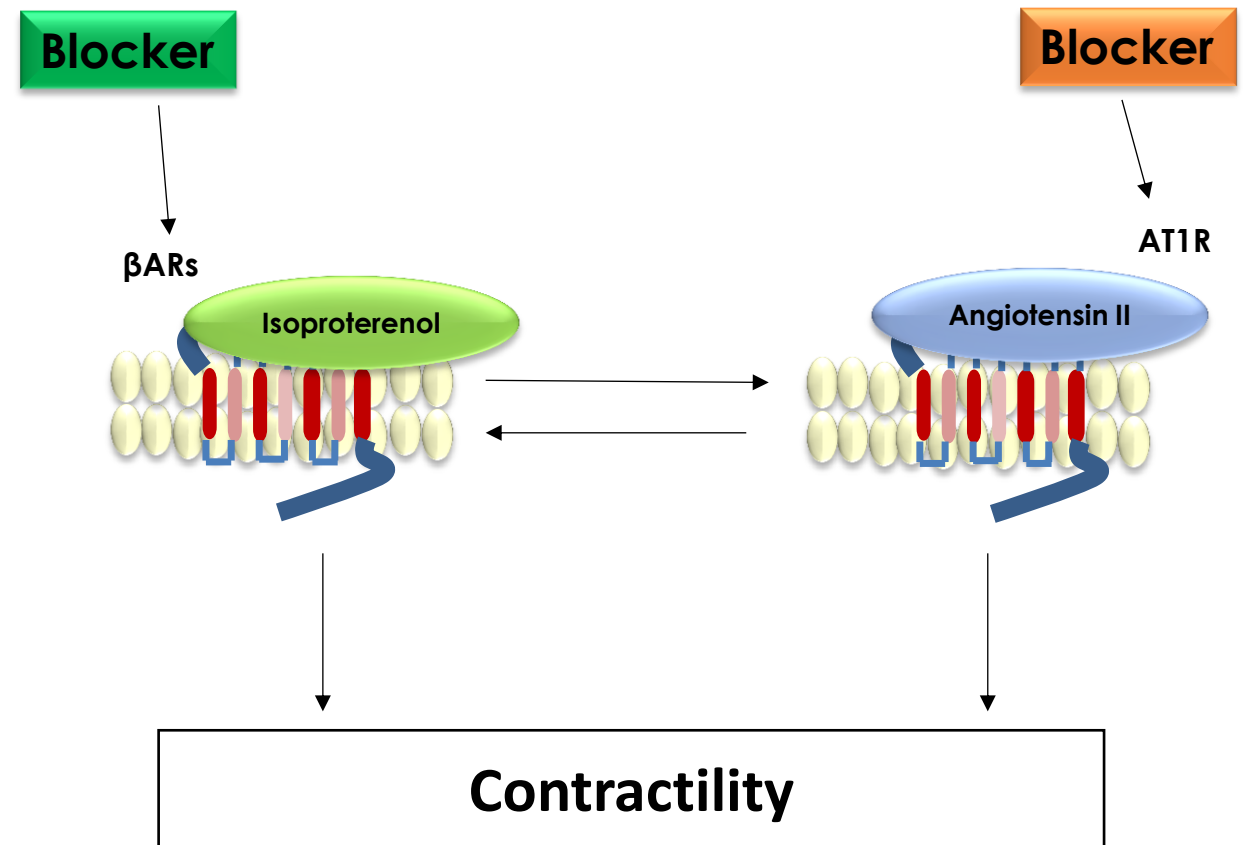
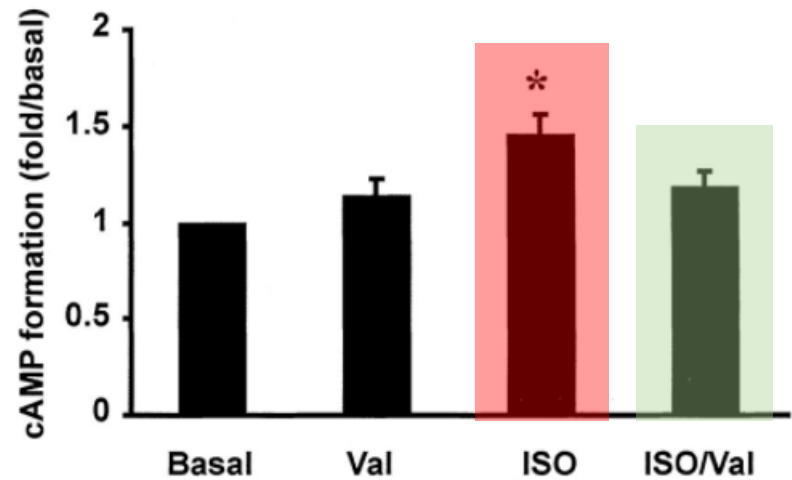
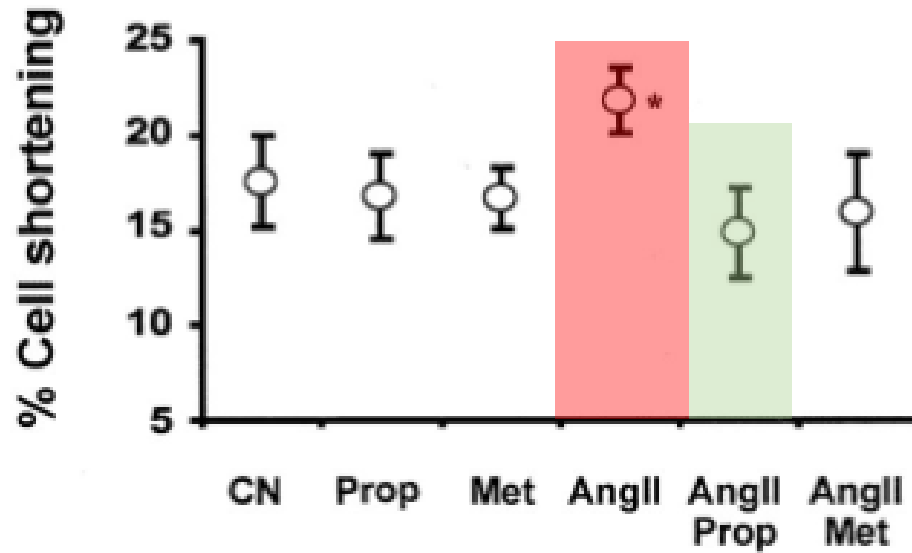


# Dual Inhibition of $\beta$ -Adrenergic and Angiotensin II Receptors by a Single Antagonist

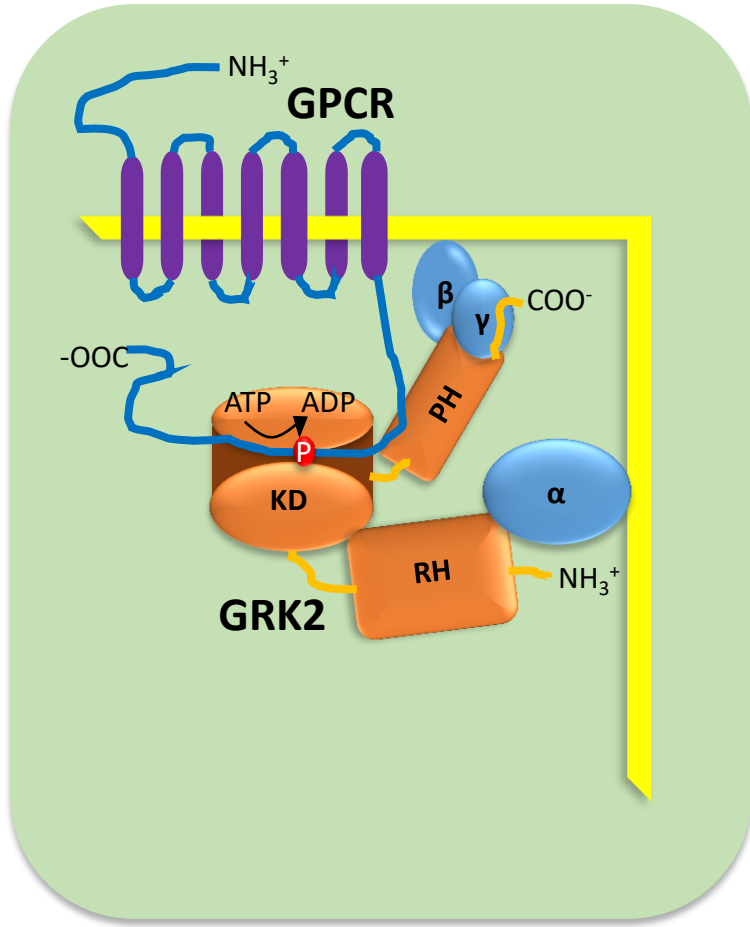
## A Functional Role for Receptor-Receptor Interaction In Vivo

Liza Barki-Harrington, PhD; Louis M. Luttrell, MD, PhD; Howard A. Rockman, MD 

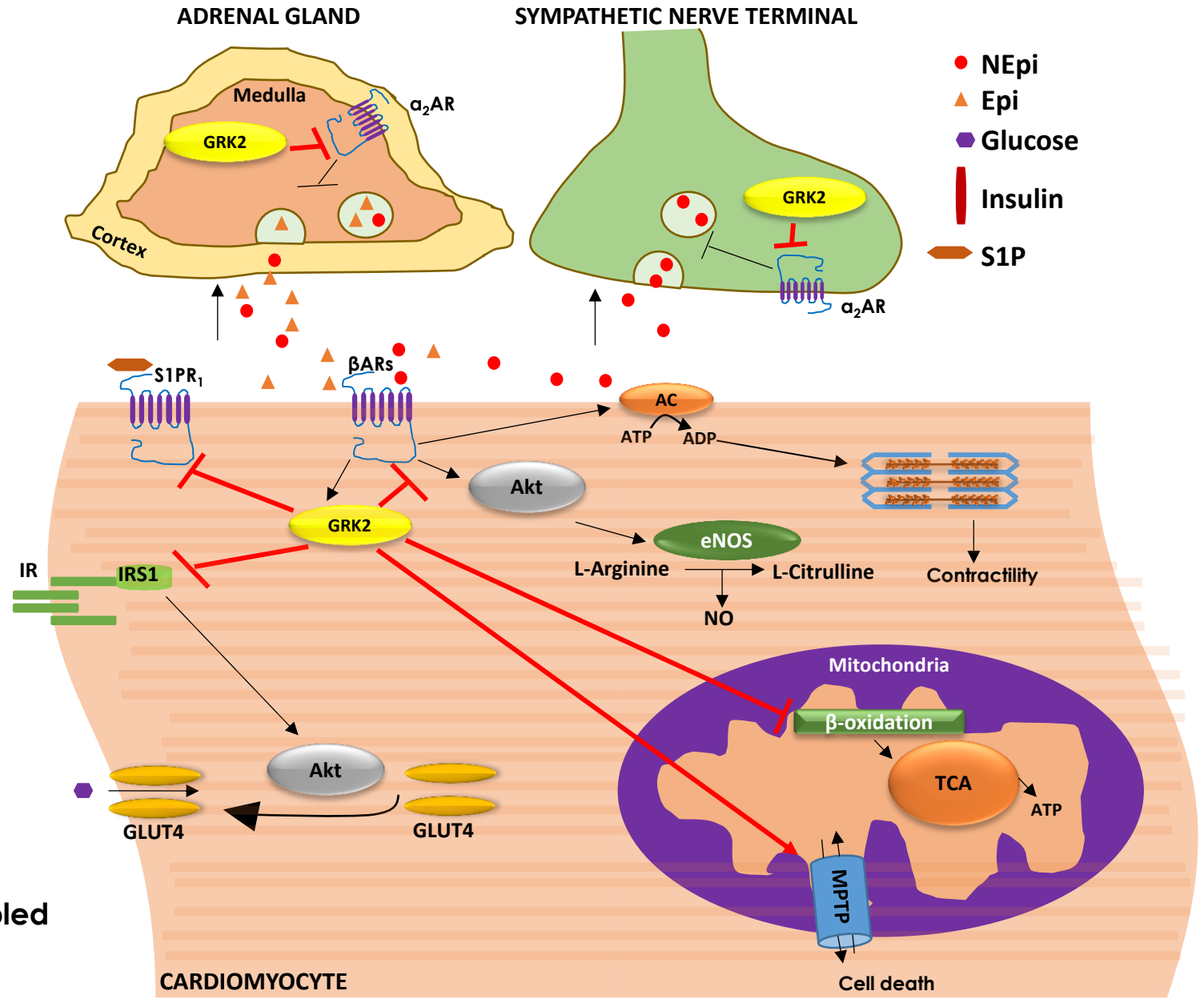
Circulation 2003



# Receptor Cross-talk: The importance of GRK2 ( $\beta$ ARK1)



Cannavo et al. Expert Opin Ther Targ 2017

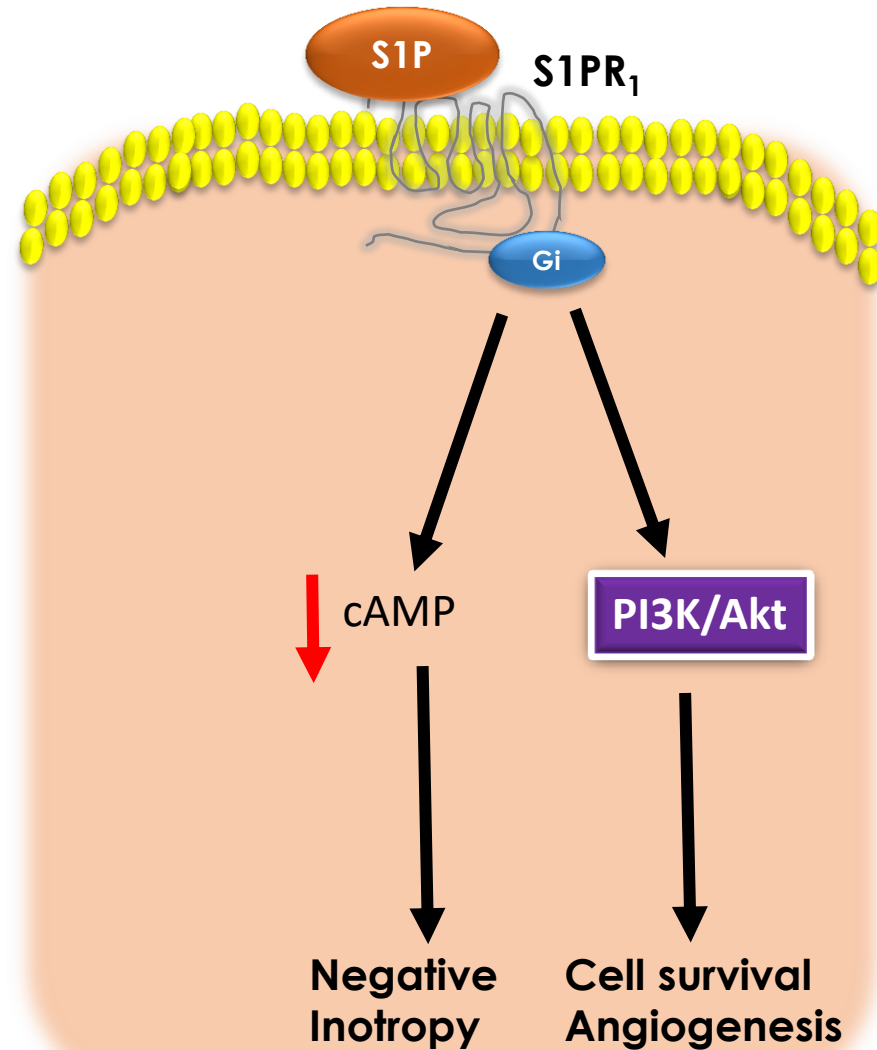


Cannavo et al. Expert Opin Ther Targ 2017

Prognostic Value of Lymphocyte G Protein-Coupled Receptor Kinase-2 Protein Levels in Patients With Heart Failure

Rengo et al. Circ Res. 2016

# Cardiac Sphingosine 1-Phosphate receptor <sub>1</sub>



Santos-Gallego et al. Circulation. 2016

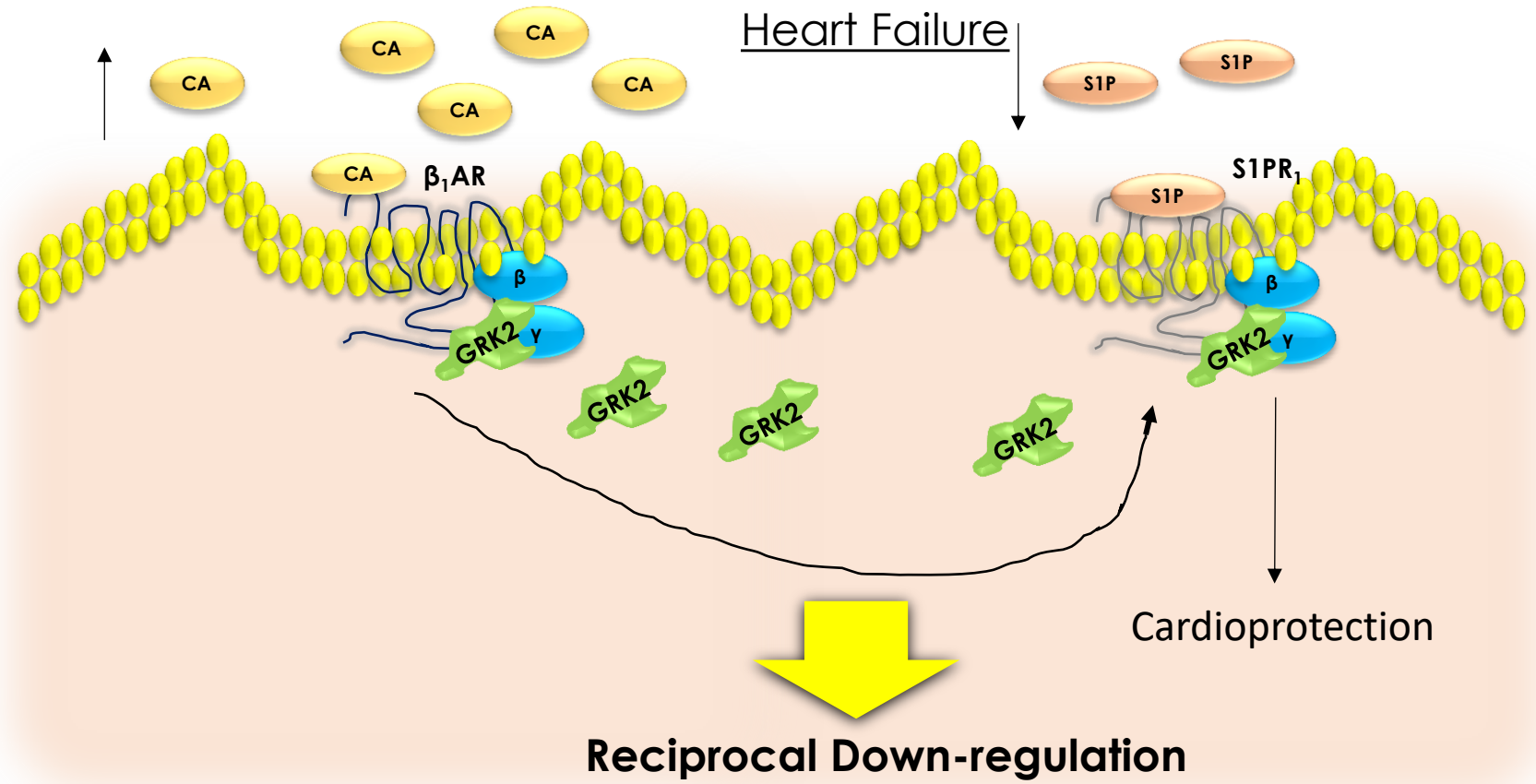
Clay et al. Dev Biol. 2016

Cannavo et al. Circulation 2013

Egom et al. J Mol Cell Cardiol. 2010

Means et al. Cardiovasc Res. 2009

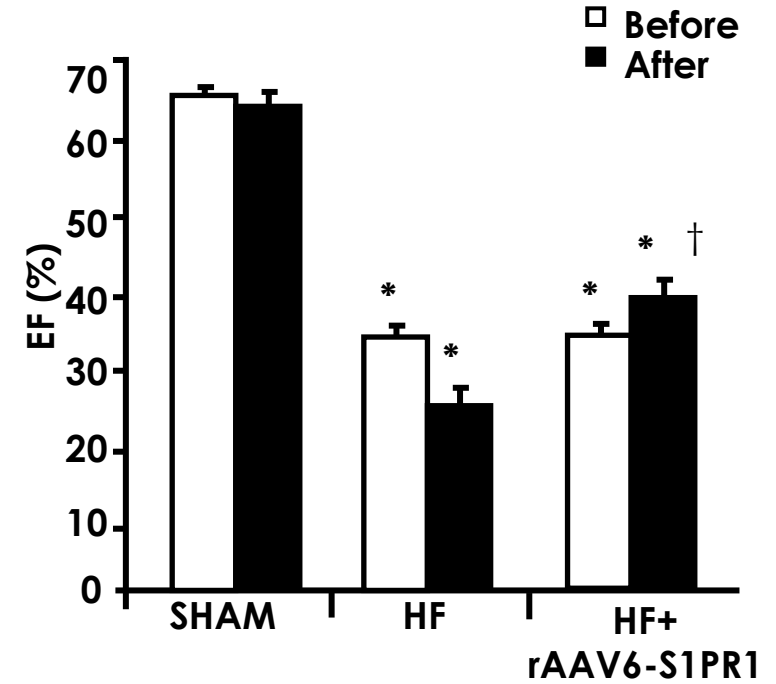
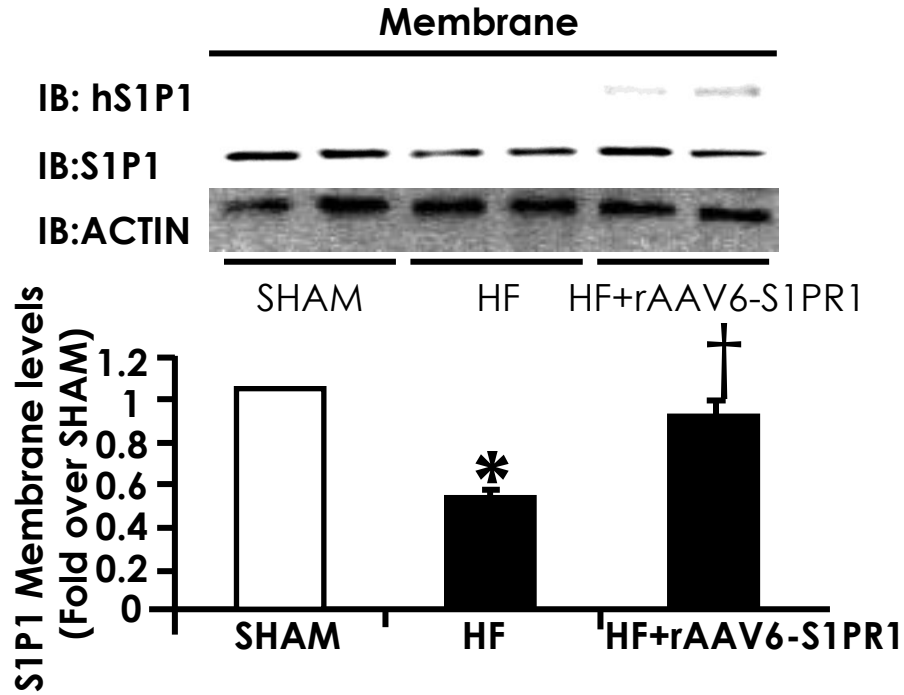
# $\beta$ 1-adrenergic receptor and Sphingosine-1-phosphate receptor 1 reciprocal down-regulation influences cardiac hypertrophic response and progression toward heart failure: protective role of S1PR1 cardiac gene therapy.



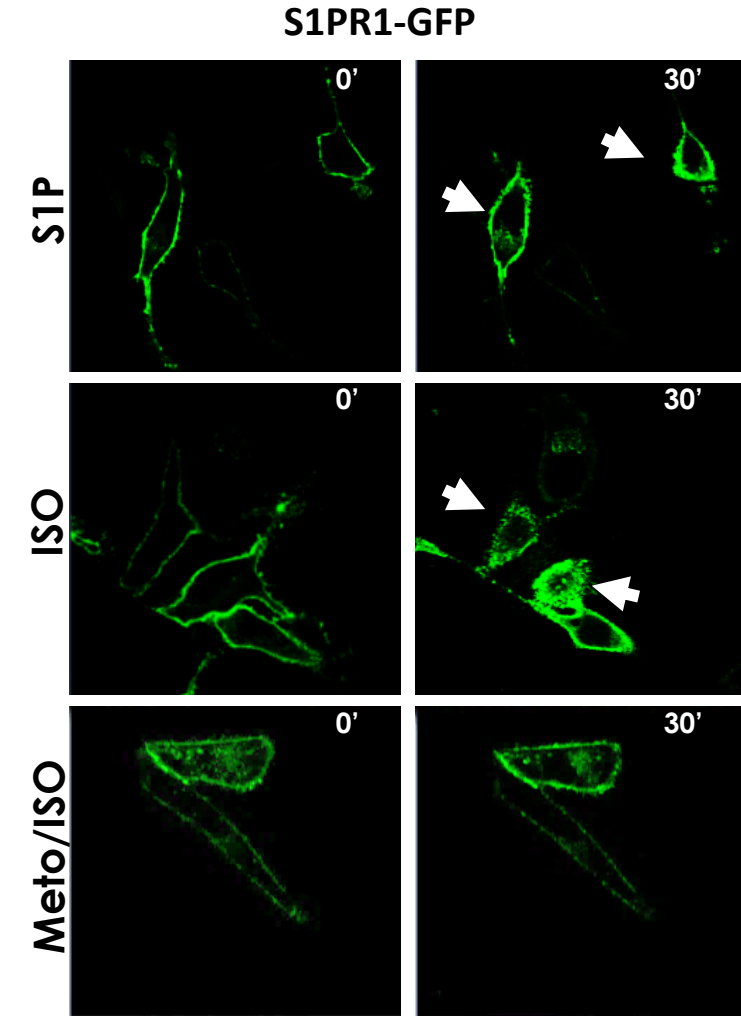
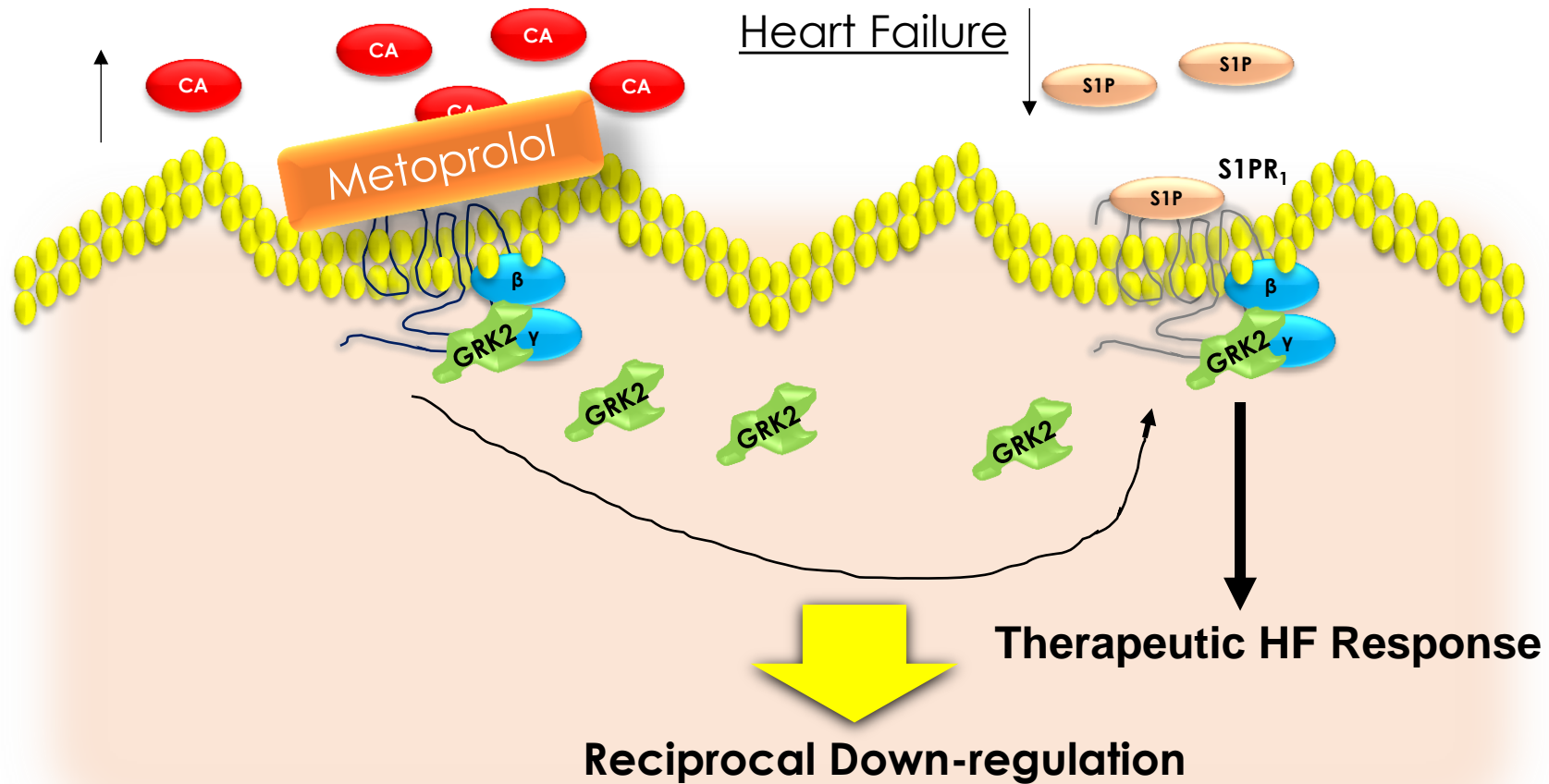
# Protective role of S1PR1 cardiac gene therapy



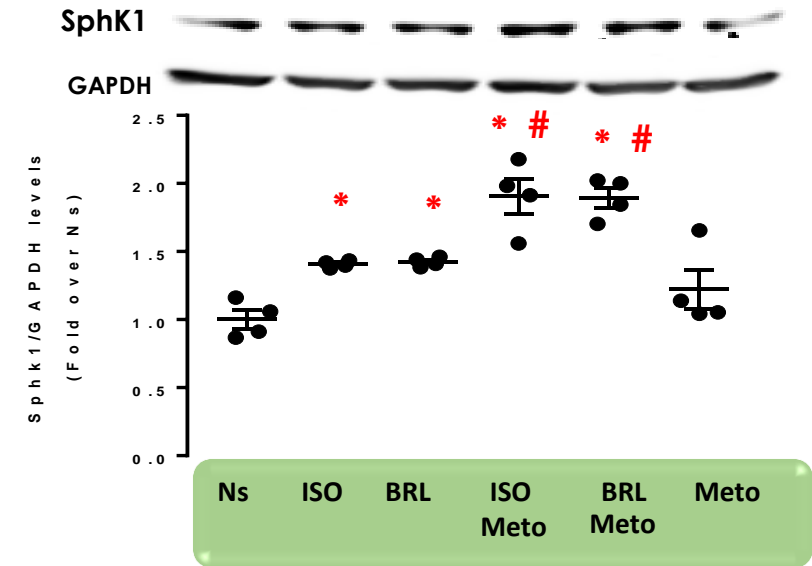
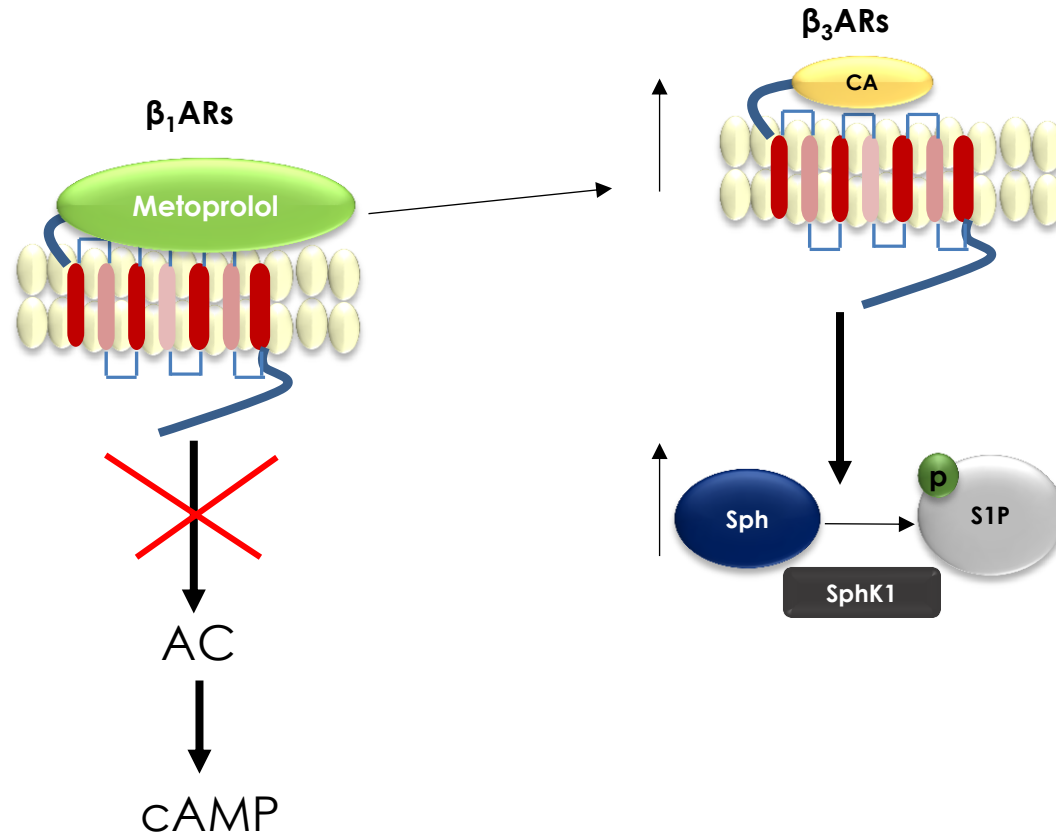
Cardioprotection



# Metoprolol blocks Catecholamine-induced S1PR<sub>1</sub> down-regulation

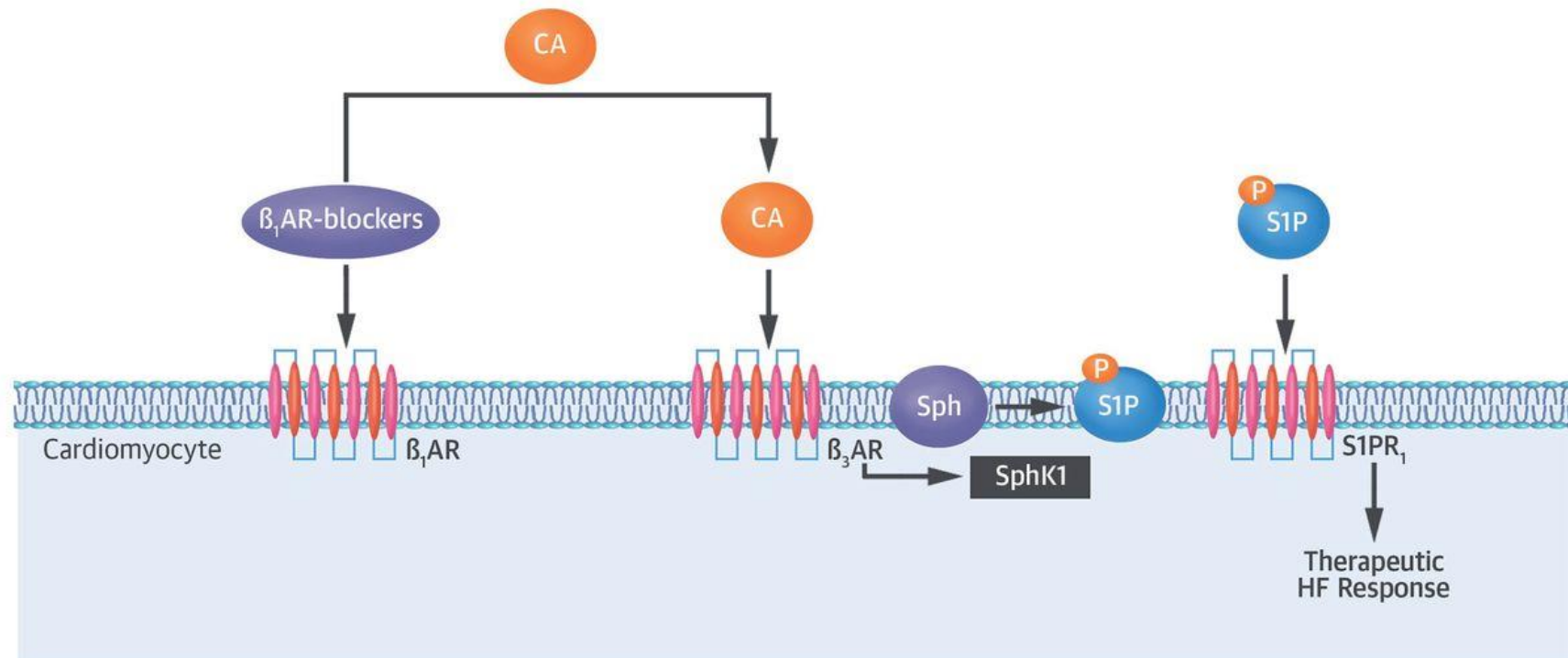


# Metoprolol enhances $\beta_3$ AR activity conferring cardioprotection via S1P

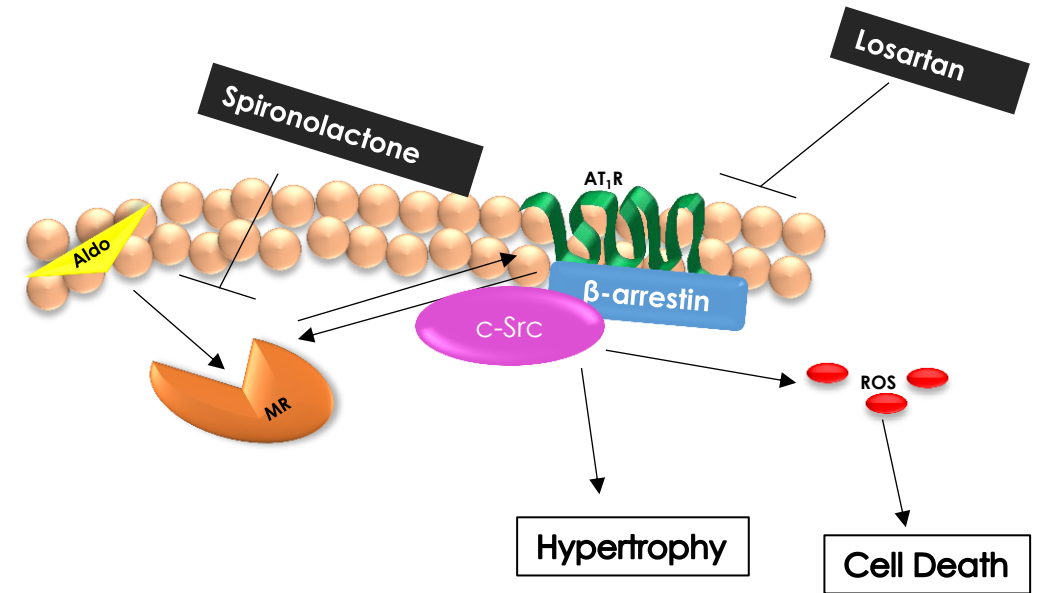
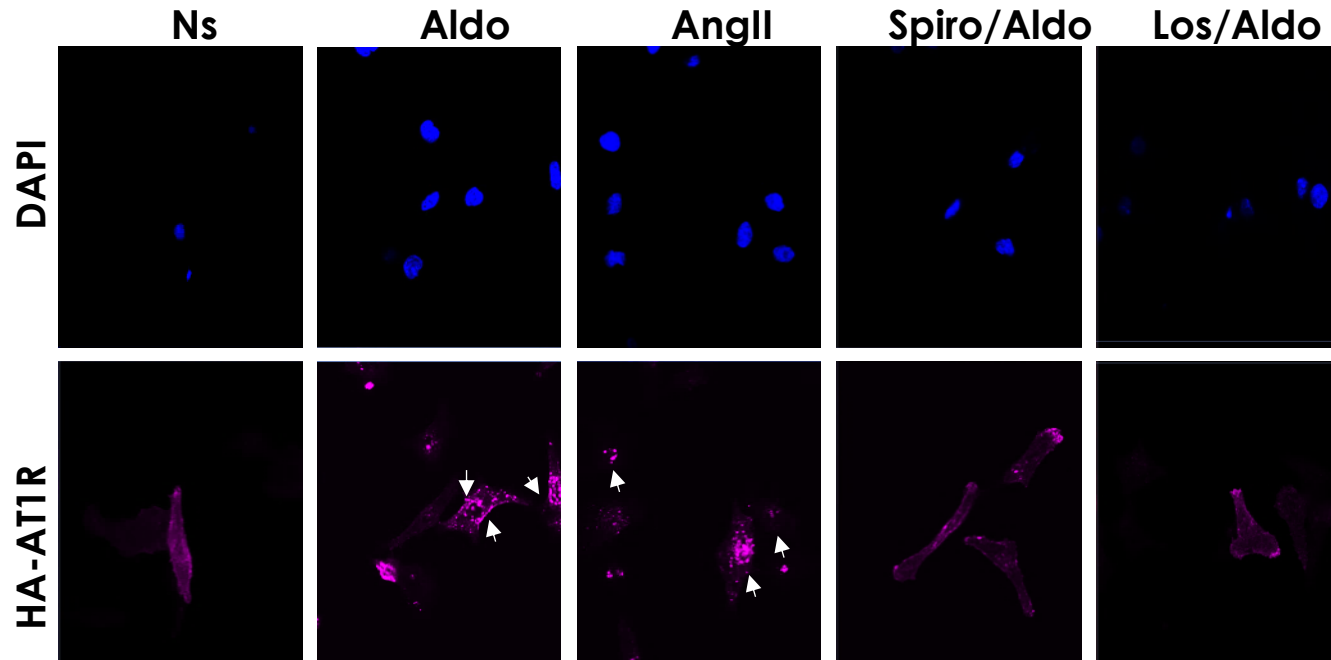


ISO =  $\beta_{1/2}$  AR agonist  
 BRL =  $\beta_3$  AR agonist

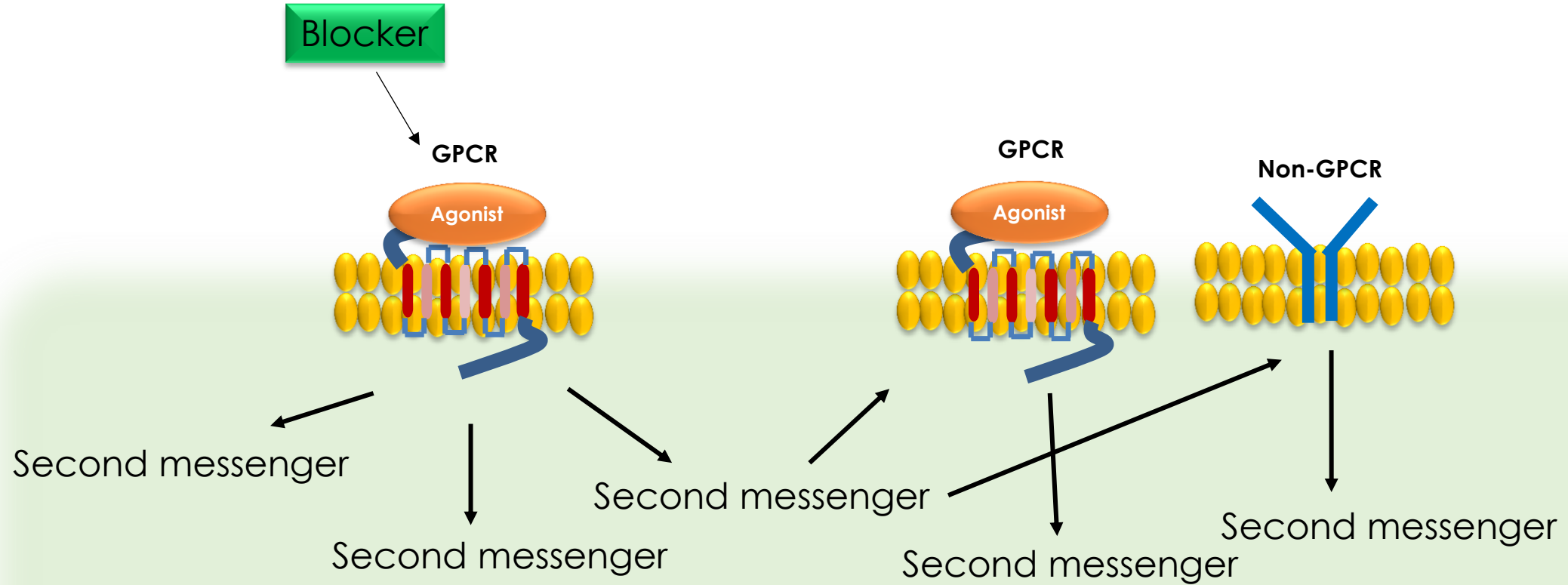
**CENTRAL ILLUSTRATION:  $\beta_1$ AR-Blocker-Dependent Activation of  $\beta_3$ AR/S1P Protective Signaling in Cardiomyocytes**



# Cross-talk between AT1R and MR in the onset of Heart failure



# Conclusion



**Receptor Cross-talk**

# Ringraziamenti



**Walter J Koch, PhD**  
**Ehre Gao, MD, PhD**  
*Alvin J. George, Student*

This work has been supported by:  
**American Heart Association-16POST30980005**



**Nicola Ferrara, MD**  
**Giuseppe Rengo, MD, PhD**  
**Dario Leosco, MD, PhD**  
*Daniela Liccardo, PhD*  
*Giuseppina Gambino, PhD*  
*Maria Loreta D'Amico, PhD*  
*Andrea Elia, MS*



**John Tesmer, PhD**



**Borjia Ibanez, MD**  
*Andres Pun-Garcia, PhD*



**Nazareno Paolucci, MD, PhD**

***“I rarely plan my research; it plans me.”***

***Max Ferdinand Perutz***

# Grazie !