54. GRK5 - Crucial Regulator in Cardiac Hypertrophy

(Lead Discovery Center)

Asset Overview

Product Type	Small molecule
Disease Area	Cardiovascular disease
Indication	Heart failure, Takotsubo, Hypertrophic Cardiomyopathy
Current Stage	Preclinical (Lead optimization)
Target	Cardiac GPCR
MoA	GRK5 is (i) a critical regulator of cardiac GPCR-coupled receptor signaling, (ii) up-regulated in heart failure caused by abnormal hypertrophic stress
Brief Description	Stress-induced GRK5 translocation leads to changes in gene expression & irreversible remodeling processes Mouse model: (i) GRK5-KO → prevention of cardiac remodeling processes, (ii) GRK5-OE* → cardiac hypertrophy Objective: Prevention of irreversible cardiac remodeling processes (maladaptation) by selective GRK5 blockade
Intellectual Property	-
Publication	-
Inventors	Johannes Backs, University Hospital of Heidelberg/Germany, K. Lorenz, ISAS, Dortmund/Germany, Axel Ullrich, Max-Planck Institute for Biochemistry, Munich/Germany, Jemincare, Shanghai/China

Highlights

- Generation of new chemical matter: kinase inhibitor screen followed by rational design-based hit-to-lead optimization
  → Stress-induced GRK5 translocation leads to changes in gene expression & irreversible re-modelling processes
  → Key criteria of lead series: single digit nM GRK5 inhibition; >300-fold selectivity over GRK2 and other kinases;
- orally bioavailable;
  → PD (in vitro): anti-hypertrophic effect in primary mouse & rat cardiomyocytes using catecholamine stimuli
  → >200 novel compounds – SAR fully understood
- PoC (in vivo): active in Takotsubo cardiomyopathy and Transverse aortic constriction (TAC) models

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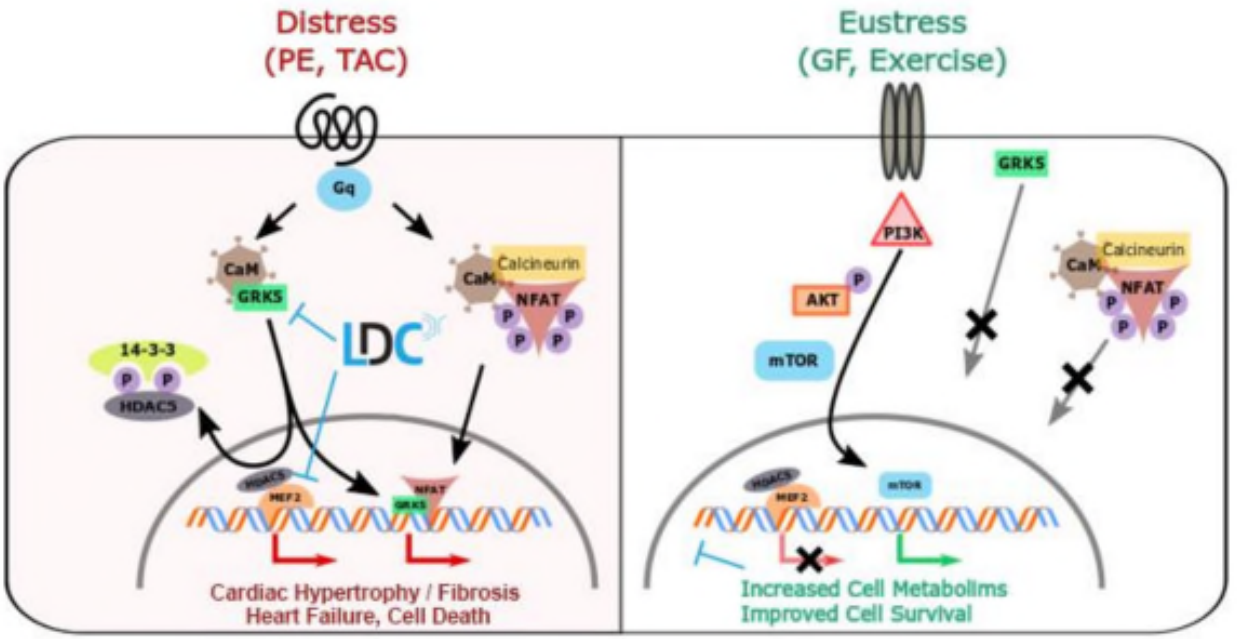
Key Data

GRK5 Inhibitors



Source: Perdue, L. A. et al. (2020). Biomacromolecules. Fig.5