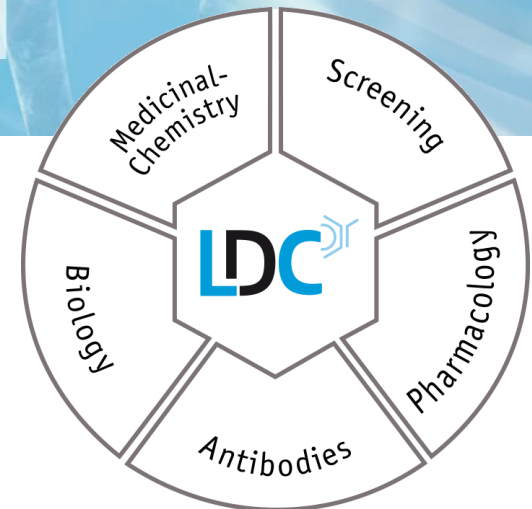


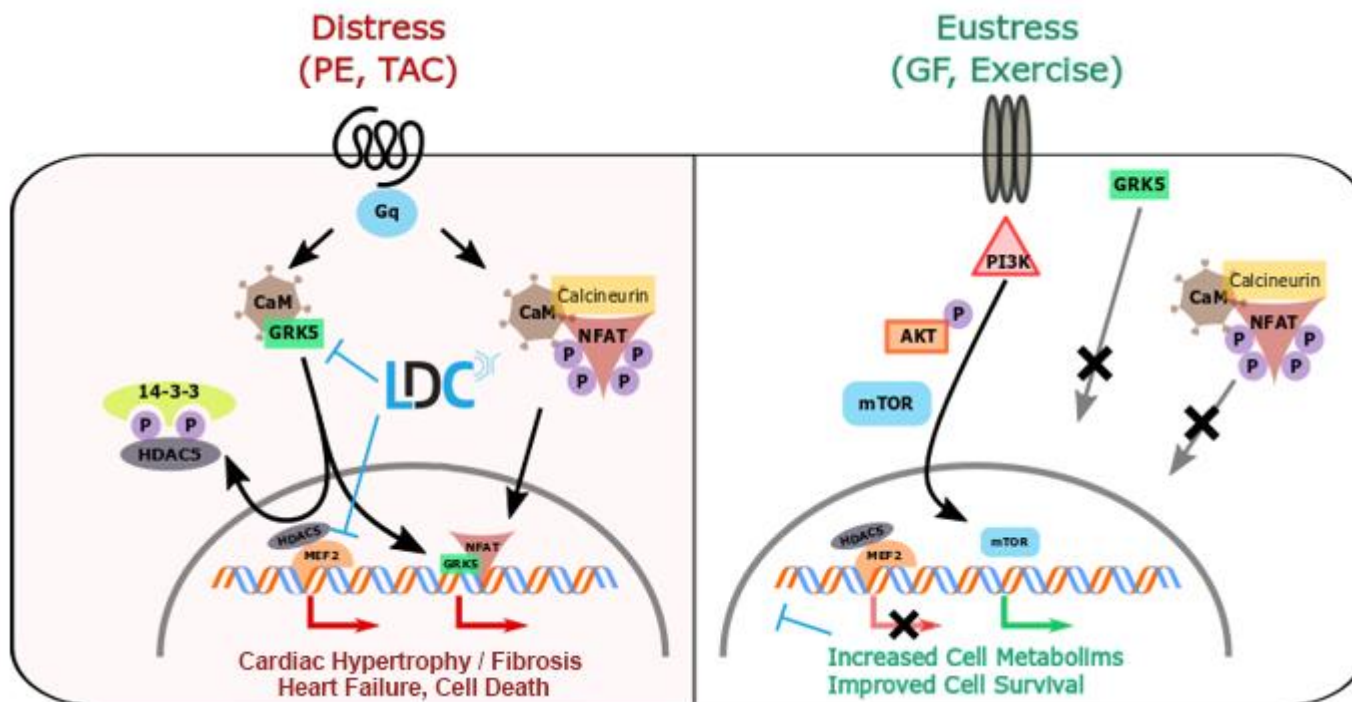


PAVING THE WAY FOR INNOVATIVE MEDICINES

GRK5 - Crucial Regulator in Cardiac Hypertrophy



GRK5 Inhibitors

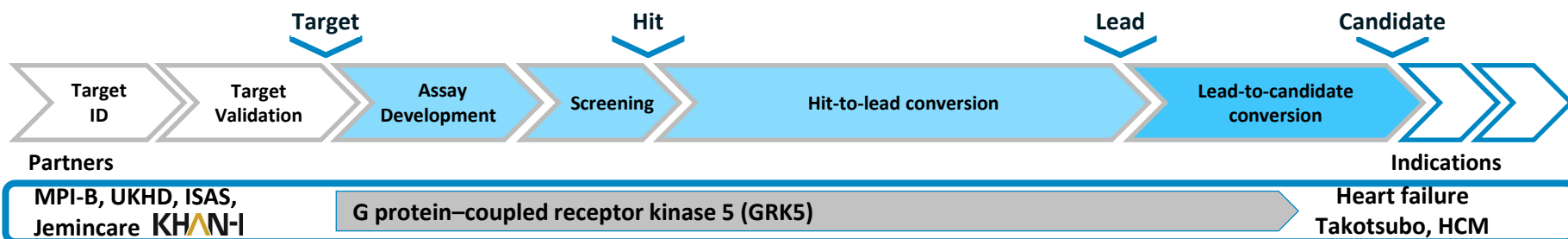


Partners:

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KHAN-I

GRK5: Executive Summary



• Target rationale

- **Basic principle:** *GRK5 is (i) a critical regulator of cardiac GPCR-coupled receptor signalling, (ii) up-regulated in heart failure caused by abnormal hypertrophic stress*
 - Stress-induced GRK5 translocation leads to changes in gene expression & irreversible remodelling processes
 - Mouse model: (i) GRK5-KO → prevention of cardiac remodelling processes, (ii) GRK5-OE* → cardiac hypertrophy
- **Objective:** *Prevention of irreversible cardiac remodelling processes (maladaptation) by selective GRK5 blockade*

• Key achievements & USPs

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

• Current activities & next steps

- *Lead Optimization in collaboration with Jemincare (Jemincare: Rights for China, LDC: RoW)*
- *LDC is responsible for all commercialization activities*
- *Nomination of a preclinical development candidate (PDC) anticipated for 2023*

* OE - overexpression



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