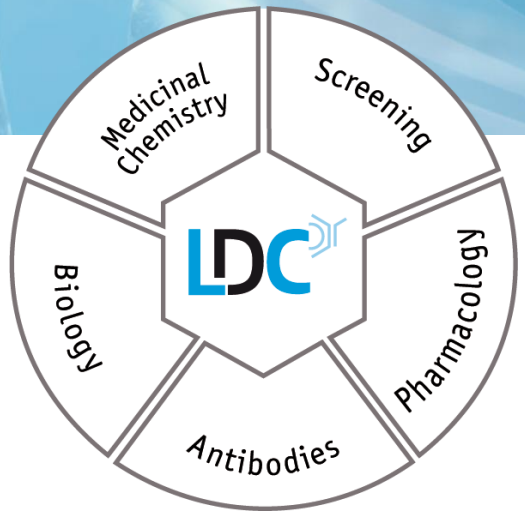
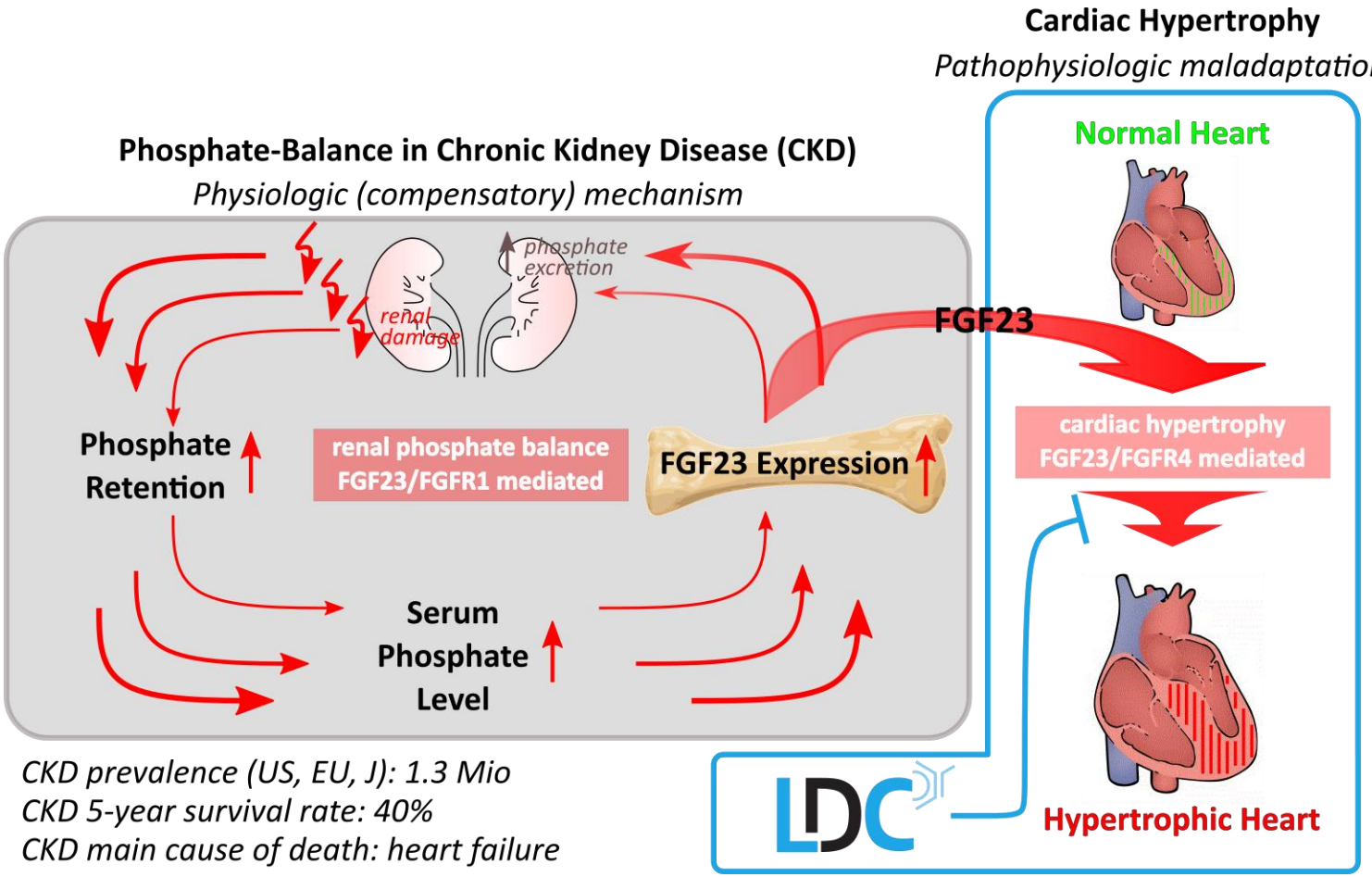
Lead Discovery Center LDC

KHAN-I

A Novel FGFR4 Antibody to Treat Cardiac Death in Chronic Kidney Disease (CKD)



FGFR4 Antibody & Heart Failure in CKD



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FGFR4 Antibody: Executive Summary

- **Target rationale**
  - ***Basic principle**: Left ventricular hypertrophy (LVH) in CKD mediated by FGF23/FGFR4 overdrive*
    - *Elevated serum phosphate levels as symptom of CKD stimulate FGF23 expression in bone*
    - *Cardiac FGF23/FGFR4 overstimulation leads to LVH and increased adverse cardiovascular events*
    - *In vivo PoP study in 5/6 nephrectomy rat model*: FGFR4-Ab prevents (i) FGF23/FGFR4 interaction, and (ii) LVH*
  - ***Aim**: Development of an antibody specifically interfering with FGFR4/FGF23 interaction without compromising FGFR1/FGF23 (phosphate level regulation) and FGFR4/FGF19 (bile acid level regulation) interactions*
- **Key achievements & USPs**
  - *Immunisation of 8 chickens and 6 rabbits completed*
    - *~20 Mio B-cells screened, and 550 FGFR4 binders identified*
    - *Characterisation of 59 recombinant purified monoclonal antibodies*
  - *Selection of several candidates for in vivo profiling – selection criteria:*
    - *Inhibition of (i) FGF23 binding to FGFR4 and (ii) FGF23-induced signalling*
    - *Lack of inhibition on FGF19-induced bile acid regulation*
- **Current activities & next steps**
  - *In vivo PoC studies in mice (with 2 candidates): FGF23 induced LVH ± FGF23-AB in progress*
  - *Selection of best possible candidate for humanization*

** A. Grabner et al., Cell Metab. 22, 1020–1032 (2015).*

Lead Discovery Center GmbH
Otto-Hahn-Straße 15
44227 Dortmund
Tel. +49.(0)231.97427000

Semmelweisstraße 5
82152 Planegg
Tel. +49.(0)89.954586201

www.lead-discovery.de